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American Journal  
of Medicine



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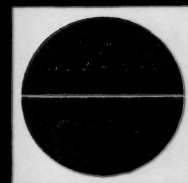
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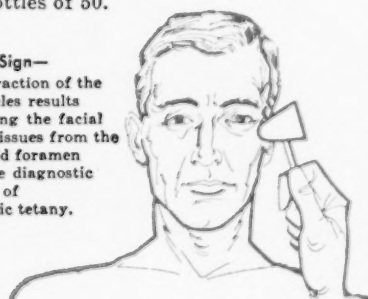
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1. Grollman, Arthur: *Essentials of Endocrinology*. Philadelphia, J.B. Lippincott Co., 2nd ed., 1947, p. 269.
2. Sandock, Isadore: Tetany and ovarian function. *J.A.M.A.*, 160:659, Feb. 25, 1956.

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**Chvostek's Sign—**  
Tonic contraction of the facial muscles results from tapping the facial nerve as it issues from the stylomastoid foramen—one of the diagnostic indications of hypocalcemic tetany.



# The American Journal of Medicine

Vol. XXV SEPTEMBER, 1958 No. 3

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Hunger and Appetite. Physiologic Regulation of Food Intake

HENRY D. JANOWITZ 327

### Clinical Studies

Subacute Hepatic Necrosis and Postnecrotic Cirrhosis Due to Anicteric Infections with the Hepatitis Virus . . . . . GERALD KLATSKIN 333

It is becoming increasingly evident that hepatic necrosis due to infection with hepatitis virus may be severe and extensive enough to result in ultimately fatal postnecrotic cirrhosis, yet throughout the prolonged early infectious phase run an insidious course with little or no jaundice and only the most general systemic manifestations. The diagnosis in the early phases obviously is elusive, and the hepatitis virus etiology of the resulting postnecrotic cirrhosis correspondingly difficult to establish. The evidence compiled in this report, however, provides a sequential relationship which supports the general conviction that postnecrotic cirrhosis may derive from anicteric viral hepatitis. There appears to be a particular susceptibility in women, and a troublesome tendency to simulate extra-hepatic biliary tract obstruction or primary biliary cirrhosis. The study is well worth a careful reading.

A Controlled Study of the Effects of L-Arginine on Hepatic Encephalopathy  
T. B. REYNOLDS, A. G. REDEKER AND PAUL DAVIS 359

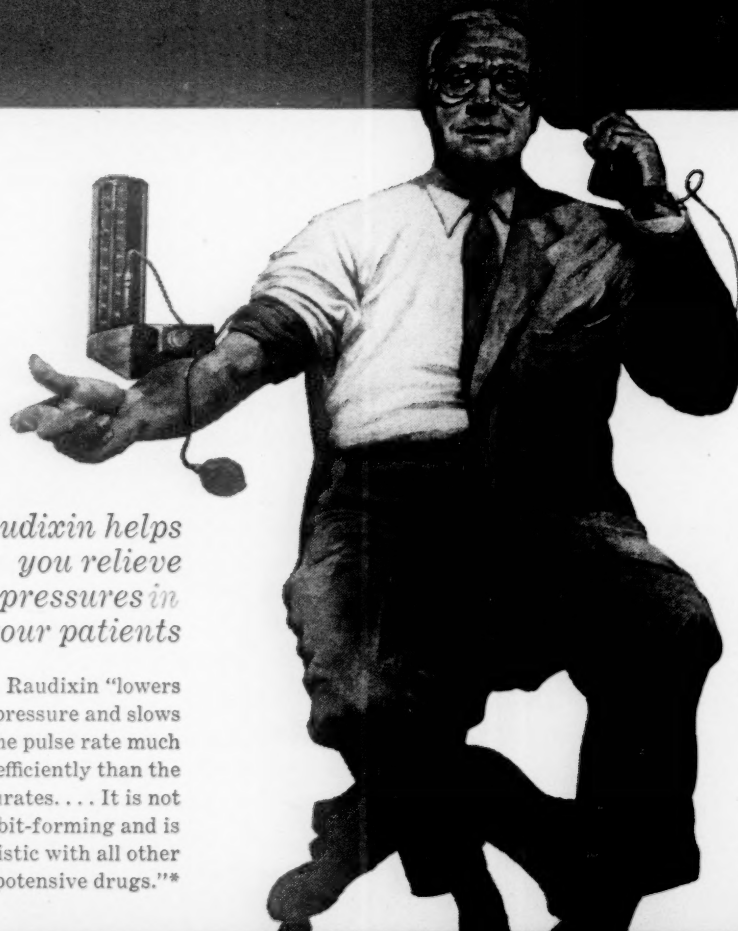
This is one of an increasing number of recent reports expressing disappointment in the efficacy of administration of L-arginine in the treatment of hepatic encephalopathy. The present study deserves special attention because unlike most earlier favorable or unfavorable reports, the observations were made under controlled conditions by the double blind technic. Encephalopathy was related in most instances to alcoholic cirrhosis with hepatic insufficiency. The results unequivocally fail to establish any significant improvement attributable to arginine under these circumstances.

Needle Biopsy of the Liver. Comparison of Initial Clinical and Histological Diagnoses, with a Note on Postbiopsy Mortality in Patients with Metastatic Neoplasm  
CURTIS J. FISHER AND WILLIAM W. FALLOON 368

Needle biopsy of the liver has become an accepted diagnostic procedure which carries a calculated risk generally considered to be permissible in selected cases. There may still be some question, however, whether the net gain in precise diagnosis and orientation in management sufficiently counterbalances the conceded hazard to which the patient is exposed. There is also doubt as to the circumstances in which laparotomy may be preferable. The present analysis of the results in 341 needle biopsies of the liver helps to assess these points. In about two-thirds of the cases the information

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derived was judged to be of diagnostic significance; in one-third of the cases the interpretation of the biopsy findings was at variance with the initial clinical diagnosis, although not always borne out by subsequent events. In the presence of extensive metastases to the liver the procedure was found to be hazardous enough to question whether laparotomy might not be preferable under such circumstances.

## Islet Cell Tumor and a Syndrome of Refractory Watery Diarrhea and Hypokalemia

JOHN V. VERNER AND ASHTON B. MORRISON 374

The association of non-insulin-secreting islet cell adenoma of the pancreas with peptic ulcer has recently received wide notice, but concomitant diarrhea, which also is present in many such cases, has not previously been sufficiently remarked upon. The present study emphasizes the occurrence of refractory watery diarrhea in association with such "benign" pancreatic adenomas, indeed as an initial and predominant manifestation. Hypokalemia develops, presumably as a result of excessive loss of gastrointestinal secretions, and this leads to renal tubular changes of the type occurring with potassium depletion, and ultimately to the patient's death. Removal of the islet cell adenoma of the pancreas is indicated, if the difficult diagnosis can be made.

## Long-Term or Maintenance Adrenal Steroid Therapy in Non-tropical Sprue

MICHAEL J. LEPORE 381

The protracted beneficial effects of long-term steroid therapy of otherwise intractable sprue are further documented in this report of six cases. Relapse invariably occurred when the dosage was reduced too far or discontinued. Except for one instance of apparent activation of tuberculosis and one patient in whom a duodenal ulcer developed and then healed in the course of steroid therapy, no untoward complications occurred in this relatively small series.

## Peroral Small Bowel Mucosal Biopsy

MAJOR ROBERT B. W. SMITH, LT. COL. HELMUTH SPRINZ,  
LT. COL. WILLIAM H. CROSBY AND COL. B. H. SULLIVAN, JR. 391

An ingenious new device to secure biopsy specimens from the gastrointestinal tract is described.

## Uropepsin and 17-Hydroxycorticoid Excretion in Normal Subjects and Patients with Peptic Ulcer during Both States of Activity and Quiescence

MARVIN H. SLEISENGER, CHARLES M. LEWIS, MARTIN LIPKIN  
AND CARL WIERUM 395

While a general correlation between urinary uropepsin excretion and gastric secretory activity has been indicated, the clinical significance and diagnostic usefulness of this relationship have not been satisfactorily established. The present careful study examines this question and makes clear that the uropepsin excretion in patients with active and inactive gastric and duodenal ulcer is, for the most part, in excess of the normal but that the large variations found seriously limit the diagnostic value of the determination. Urinary uropepsin excretion was found to be increased in states of adrenocortical hyperactivity. Estimations of 17-hydroxycorticoid excretion in patients with duodenal ulcer, however, failed to give any indication of adrenocortical hyperactivity.

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**AN AMES  
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*which patients  
with noncalculous  
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Source—Lichtenstein, M. E.: GP 16:114 (Oct.) 1957.

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## Zoxazolamine. Physiological Disposition, Uricosuric Properties

J. J. BURNS, T. F. YÜ, LAWRENCE BERGER AND ALEXANDER B. GUTMAN 401

Zoxazolamine, introduced and employed as a muscle relaxant in spastic states, was found to have potent uricosuric properties. The drug is rapidly absorbed from the gastrointestinal tract and is converted to at least two metabolites, which are described. Renal clearance studies indicate marked suppression of tubular reabsorption of urate, even in small doses, with increased urinary urate excretion and a sharp fall in serum urate levels. This effect is of pharmacologic interest because zoxazolamine differs so markedly in structure from other uricosuric agents.

## Review

### Clinical Diagnosis of Systemic Lupus Erythematosus

R. ARMAS-CRUZ, J. HARNECKER, G. DUCACH, J. JALIL AND F. GONZALEZ 409

This is an account of the clinical and laboratory features of 108 cases of systemic lupus erythematosus observed in Chile. It is apparent that the manifestations of the disease as it occurs there do not differ appreciably from the disease encountered elsewhere.

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There have been many important recent advances in knowledge of the biochemical aspects of normal and abnormal brain metabolism, and these are reviewed informatively in the present article. The authors discuss the neurolipoidoses and other inborn errors of metabolism from this point of view, the demyelinating disorders, the effects of aging, of nutritional deficiencies and of various endogenous and exogenous poisons. They also consider the action of narcotics, anesthetics, tranquilizers and "energizers," all in terms of alterations of nerve cell energetics, transport of metabolites or interference with specific brain enzyme systems. It is apparent that a solid basis is being laid for the ultimate understanding of presently obscure diseases of the central nervous system.

## Clinico-pathologic Conference

### Total Body Radiation in Acute Monocytic Leukemia

430

Clinico-pathologic Conference (Washington University School of Medicine).

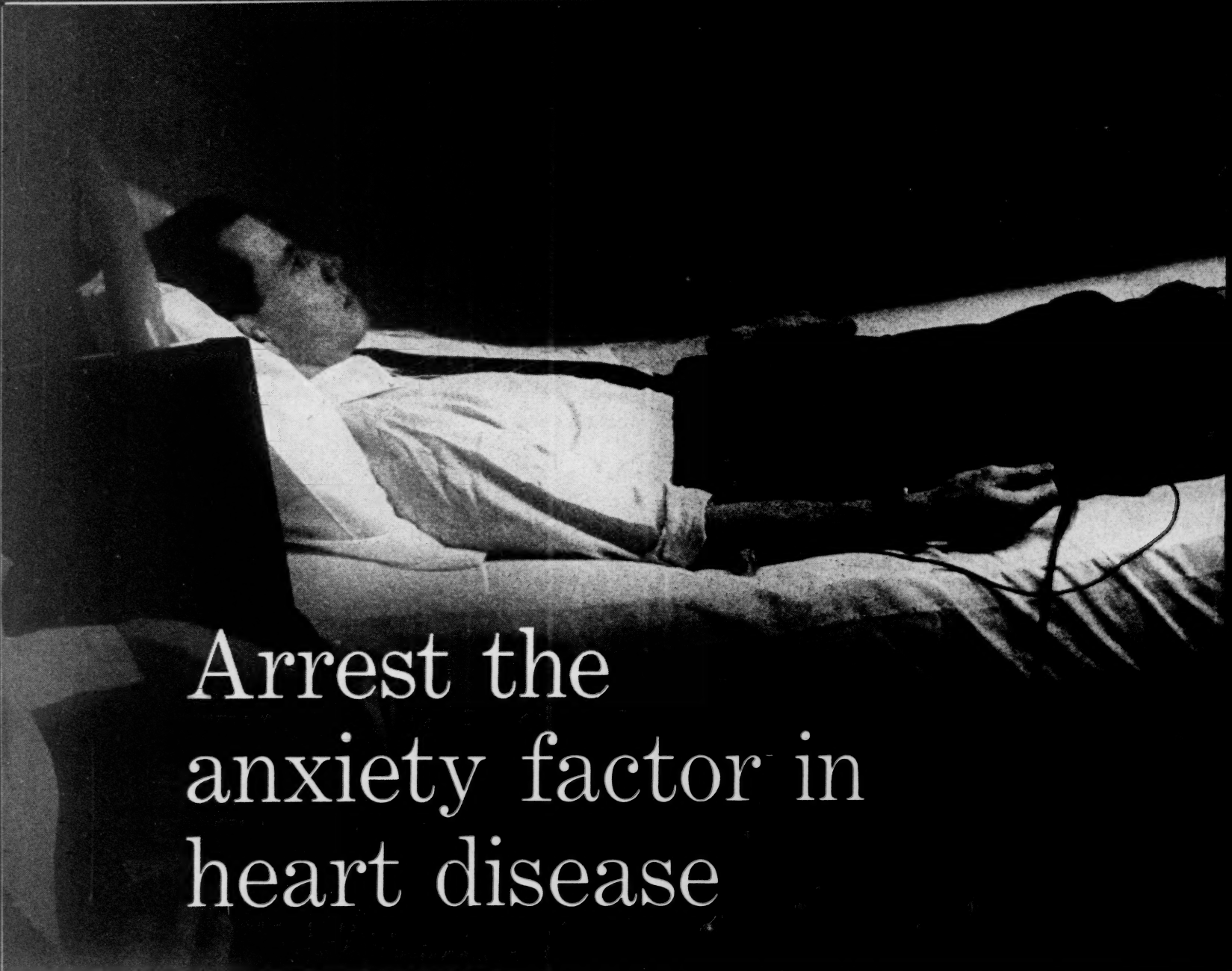
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NORTON SPRITZ, GEORGE L. FRIMPTER, WARREN S. BRAVEMAN  
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A case of persistent atrial tachycardia with atrioventricular block is presented. This arrhythmia ordinarily is due to digitalis intoxication but this case was an exception and, indeed, therapy with digitoxin was quite effective. The role of potassium in this condition is discussed.

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- Intestinal Malabsorption Following Temporary Occlusion of the Superior Mesenteric Artery . . . . R. A. JOSKE, MUNIR H. SHAMMA'A AND G. D. DRUMMEY 449

Two cases are cited in which, shortly after surgical removal of an embolus or thrombus acutely occluding the superior mesenteric artery, evidences of the malabsorption syndrome appeared. No segment of the small bowel was resected. This experience raises pertinent questions as to the role of ischemia in some cases of the malabsorption syndrome.

- Steatorrhea Associated with Ulcerogenic Tumor of the Pancreas  
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A difficult diagnostic problem ingeniously explained.

- Clinical and Histological Observations in Fatal Non-tropical Sprue  
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- Idiopathic Hypoparathyroidism Presenting as a Psychosis and Complicated by Chlorpromazine Jaundice . . . BERNARD J. B. YIM AND JOHN R. JAENIKE 478

An interesting and well studied case.

- Haemodialysis in Acute Acetylsalicylic Acid Poisoning  
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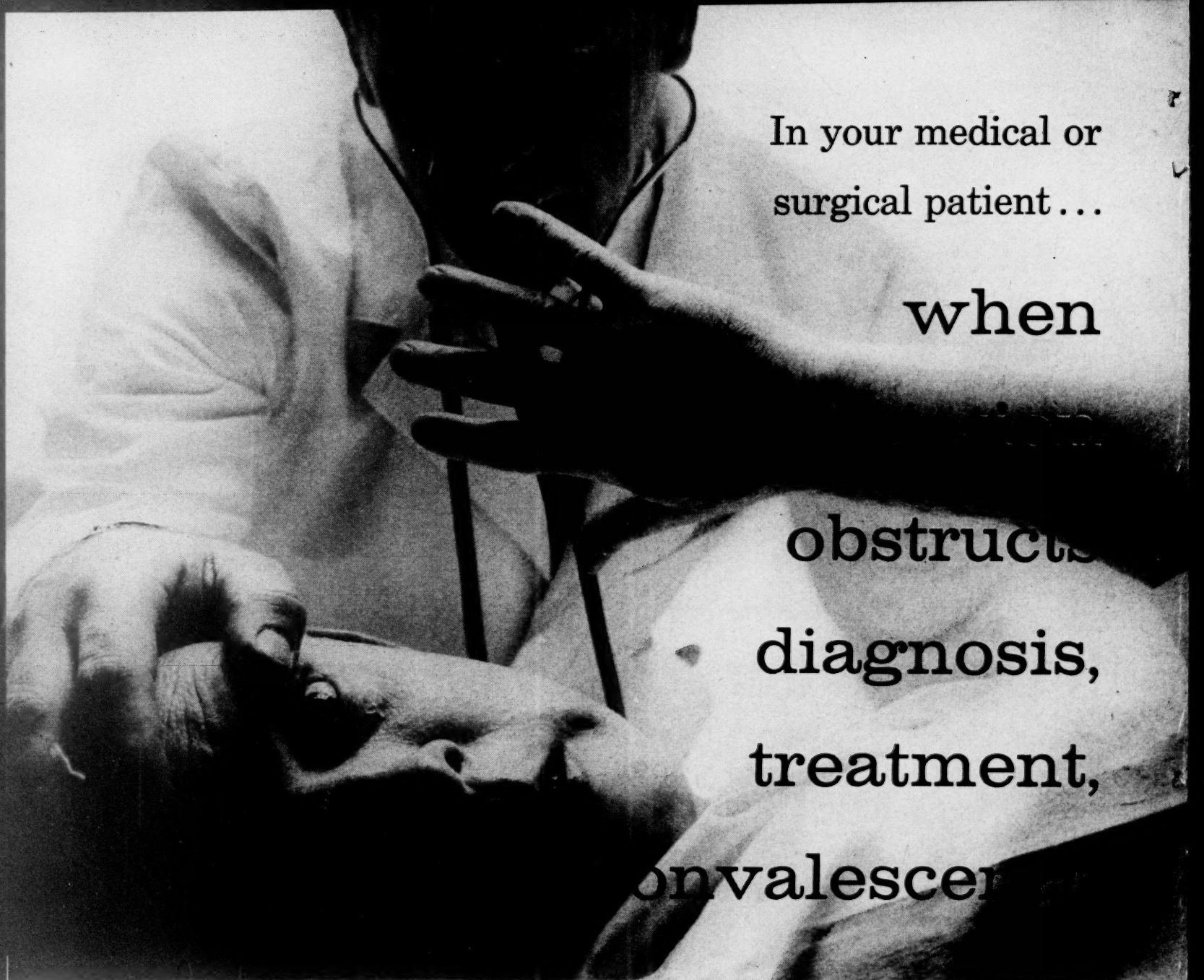
A striking example of response of acute salicylate intoxication to hemodialysis, now recognized as the most effective treatment available in severe cases.

- Xanthoma Tuberosum. A Six-Month Control Study . . . LEONARD BRESLAW 487

Working with limited facilities, this young investigator has managed to carry out a fairly extensive study of a patient with essential hypercholesterolemia and xanthoma tuberosum, including the effects of fat restriction and of administration of estrogens and heparin.

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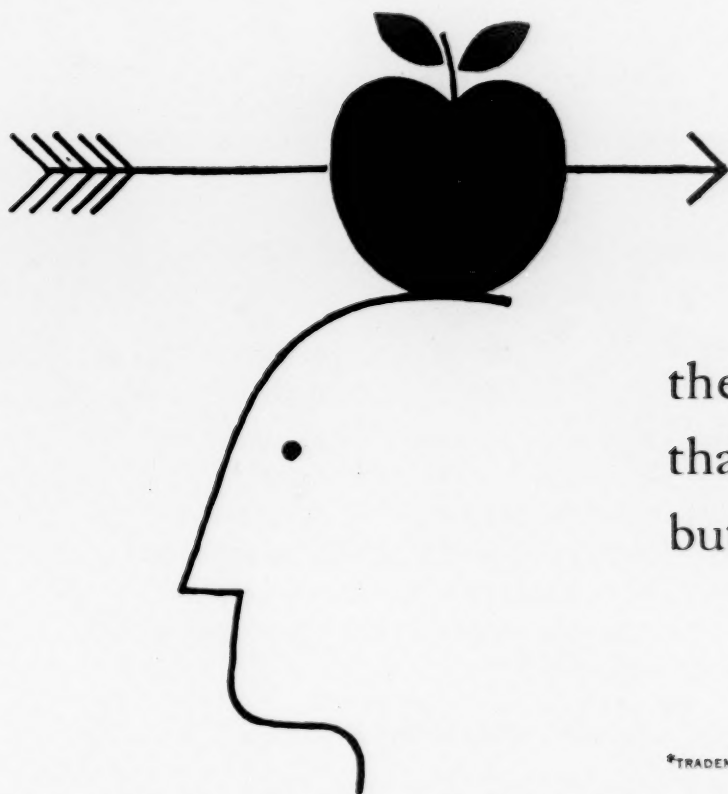
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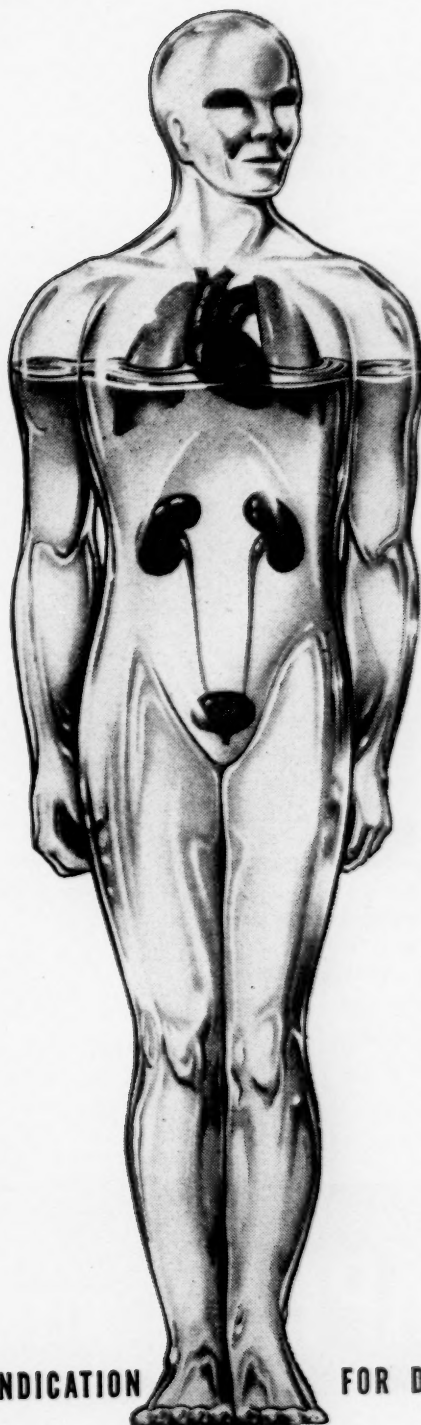
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1. Moyer, J. H., et al.: A.M.A. Arch. Int. Med. 96:530, 1955. 2. Moyer, J. H., et al.: South. M. J. 50:499, 1957. 3. Smirk, F. H., and McQueen, E. G.: Lancet 2:115, 1955. 4. Winton, S. S.: Internat. Rec. Med. 170:665, 1957. 5. Malamud, W., et al.: Am. J. Psychiat. 114:193, 1957.

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1. Van Gasse, J. J., and Miller, R. F.: Current Concepts on the Etiology and Management of Atherosclerosis, Scientific Exhibit, A.M.A. Meet., June 3-5, 1957, New York.
2. Farquhar, J. W., and Sokolow, M.: Circulation 17:890, 1958.
3. Kinsell, L. W., et al.: Lancet 1:334, 1958.
4. Malmros, H., and Wigand, G.: Lancet 2:1, 1957.
5. Van Itallie, T. B.: J. Am. Dietet. A. 34:248, 1958.

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# ORINASE

***BREAKTHROUGH IN DIABETES***

# **THE STORY OF ORINASE**

# ORINASE

**BREAKTHROUGH IN DIABETES**

When Orinase was first introduced, it was hailed primarily for the increased flexibility it lent to diabetic management, and for its patient benefits. The extensive experience of the past year has confirmed that Orinase is both safe and effective in the majority of adult, stable diabetics. But we now know that the significance of Orinase goes even further. Indeed, the new light Orinase has shed on our understanding of diabetes makes its advent a breakthrough comparable to the discovery, in 1889, that the diabetes syndrome rapidly develops following removal of the pancreas, and to the isolation of insulin in 1921.

Before Orinase, research in diabetes was moving ahead slowly. Pathogenesis of the disease remained an enigma, and the mechanism of insulin action continued to elude investigators. Nor was any explanation forthcoming for the different types of diabetic syndromes, the progressive nature of the disease, or for the wide range of insulin requirements.

Clinically, too, there was much to be desired: the lifelong regimen of daily injections, the rigid meal schedules, and, above all, the constant threat of hypoglycemia. To the patient, these meant a life centered around his disease; to the physician, the ever-present danger of complications.

And now, what are the circumstances one year after the introduction of Orinase? In briefest summary, this is where the evidence points:

**1**

*Diabetes mellitus does not appear to be a single pathological entity. There are several types of diabetic disorders. The most common is "Orinase-positive" diabetes, in which administration of Orinase induces release and utilization of the patient's endogenous insulin.*

**2**

*In "Orinase-positive" diabetics, Orinase achieves better control than injections of exogenous insulin.*

## Facts and Figures

# ORINASE

## ONE YEAR AGO-1957

Orinase was officially released for prescription on June 3, 1957. Prior to its release, it had been thoroughly and painstakingly tested in more than 20,000 patients.

**NUMBER OF PATIENTS ON ORINASE:**

20,000

**CRITERIA OF PATIENT SELECTION:**

Adult, stable diabetes  
(onset around 40 years of age)

**INCIDENCE OF SIDE EFFECTS:**  
(transitory skin rash, nausea, etc.)

Only 3%

**TOXICITY:**

None

**ESSENTIAL CONDITION  
FOR RESPONSE TO ORINASE:**

Functional pancreas

**PRIMARY MODE OF ACTION OF ORINASE:**

Unknown

**CONTRAINDICATIONS:**

Juvenile diabetes...brittle diabetes...history of coma, acidosis, or ketosis...fever... severe trauma...gangrene...diabetes adequately controlled by diet alone.

## ONE YEAR LATER-1958

Today, Orinase is a routine therapeutic agent in the management of hundreds of thousands of diabetics. Numerous clinical observations confirm its efficacy and have brought to light many new, additional benefits of Orinase therapy.

Over 300,000

Age: 40+ (at onset)

Insulin: 40- (daily requirements)

*These are typical criteria for the candidate most likely to respond to Orinase. However, diabetics with an earlier development of the disease also deserve a careful trial with Orinase, because Orinase has been found effective in many of the 20 to 40 age-of-onset diabetics.*

Approximately 3% (side effects continue to be mild and transitory—drug withdrawn for these effects in only 1.6%)

None

Functional beta cells of the pancreas

In the presence of a functional pancreas, Orinase effects the production and utilization of *native* insulin via *normal* channels.

Juvenile diabetes...brittle diabetes...history of coma, acidosis, or ketosis...fever...severe trauma...gangrene...diabetes adequately controlled by dietary restriction alone.

## Objective advantages of Orinase

Intensive diabetic research, stimulated by the introduction of Orinase, has led many investigators to revise the very concept of diabetes as a single clinical entity, and to coin the term "*Orinase-positive*" diabetes. Oral therapy of "*Orinase-positive*" diabetics presents the following advantages:

### **Better control of diabetes**

*Orinase-responsive* patients show more stable blood sugar levels and less glycosuria on Orinase than on insulin. Because Orinase acts via *endogenous* insulin, daily control of diabetes is smoother; "peaks and valleys" typical of exogenous insulin are leveled out.

### **Greater freedom from hypoglycemia**

Patients on Orinase rarely experience hypoglycemic reactions. Even when hypoglycemia does occur, it is milder and more amenable to therapy than insulin (hypoglycemic) reactions.

### **Side effects—few and minor**

Side effects attributable to Orinase occur in about 3% of cases, and only half of these necessitate withdrawal of Orinase. Most common are skin rashes or mild G.I. upsets.

### **No known toxicity**

Careful observations of large series of patients maintained on Orinase for more than two years revealed no damage to the liver, blood, kidneys, or pancreas. Orinase is not goitrogenic.

### **Painless management of diabetes**

Simple, easy, oral administration eliminates subcutaneous fat atrophy and frequent allergic reactions to insulin.

### **No increase in insulin requirements**

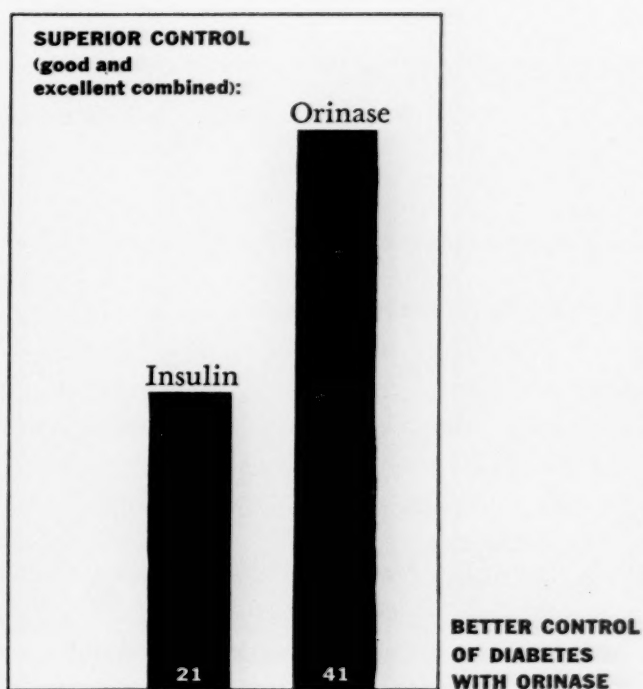
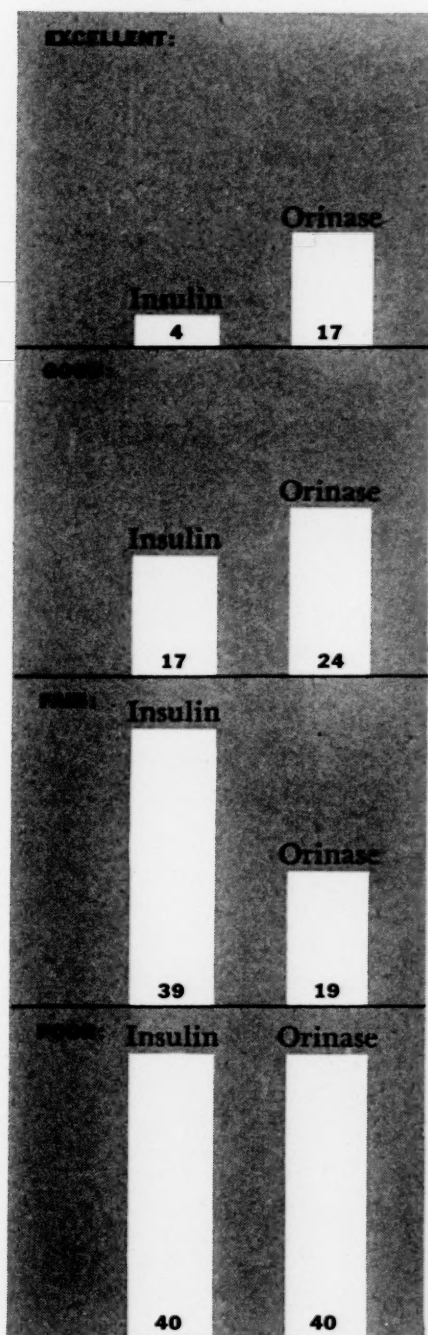
Even after prolonged Orinase therapy, patients scarcely ever show any increase in insulin requirements. In fact, such increase on Orinase is *less common than on insulin*.

### **No impairment of diabetic status**

Orinase therapy does not aggravate the underlying diabetic pathology. In some cases, there may be an actual improvement or even a remission.

**QUALITY OF DIABETIC CONTROL IN  
100 PATIENTS ON ORINASE COMPARED  
WITH CONTROL ON INSULIN<sup>1</sup>**

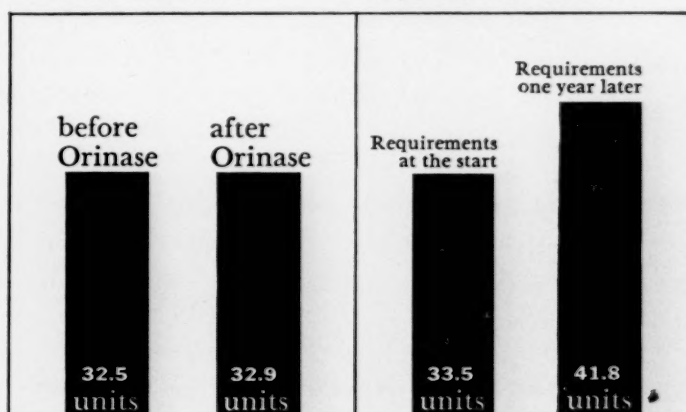
Control rating:



**NO INCREASE IN INSULIN REQUIREMENTS ON ORINASE<sup>2</sup>**

*Change in average insulin requirements of 30 diabetics resuming insulin after 1-15 months on Orinase*

*Change in average insulin requirements of 100 diabetics after one year of insulin alone*



1. Based on the data of McKendry, J. B. R.; Kuwayti, K., and Sagie, L. A.: *Canad. M. A. J.* 77:429 (Sept. 1) 1957.

2. Based on the data of Pfeiffer, E. F.: *J. Endocrinol.* 15:xlvi (June) 1957.

## Subjective advantages of Orinase

"The extreme satisfaction of patients whose conditions are now controlled with tolubutamide is immeasurable."

Breneman, J. C.: *J.A.M.A.* 164:627 (June 8) 1957.

### **ORINASE HELPS TO CORRECT MAJOR DISLOCATIONS IN THE LIFE PATTERN OF DIABETICS**

#### **Orinase tends to restore emotional balance**

Diagnosis of diabetes, usually coming late in life and carrying with it a long sentence of daily fear and anxiety, profoundly upsets the emotional balance of the average patient. Adjustment to radical changes in daily living is difficult. Daily injections, special meal schedules, and new limitations on activities make the patient feel "set apart." Oral therapy simplifies life, brings it closer to normal, helps restore a cheerful, hopeful outlook.

#### **Sense of personal freedom regained on Orinase**

No longer tied to a refrigerator, sterilizing apparatus, nearest restaurant, and rigid schedules, a diabetic on Orinase can enjoy travel and a variety of personal activities, free from the tyranny of the clock and the threat of hypoglycemia.

#### **Orinase makes diabetes easier on the patient's family**

With no dependence on members of the family for diabetic care, the patient can resume a more normal place in the family circle.

#### **Orinase permits occupational continuity**

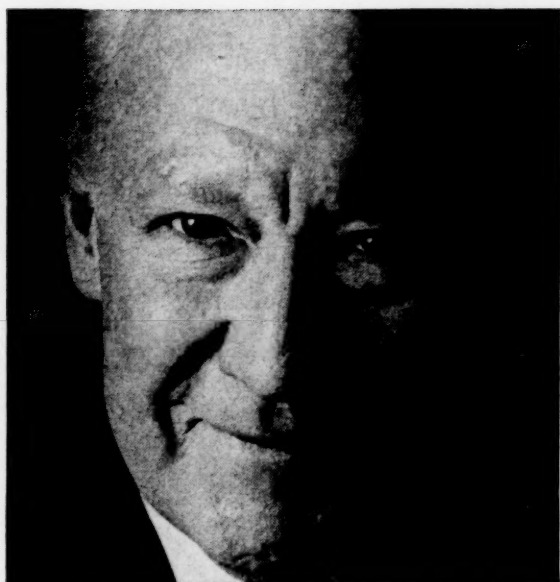
Because of the hazards of hypoglycemic shock, some diabetics are forced to give up their customary occupations, or must limit and curtail their working hours—as may be the case with traveling salesmen, business executives, and others with unpredictable work schedules. On Orinase, patients usually can continue their normal occupations.

#### **Normal social life made possible by Orinase**

"Orinase-positive" diabetics can visit their friends, without the embarrassing necessity of meals at special hours...can participate in community life and social events in a more normal fashion.

#### **Stability and sense of well-being on Orinase**

Patients report an increased sense of stability and well-being...they are less irritable...their mood and outlook are improved.



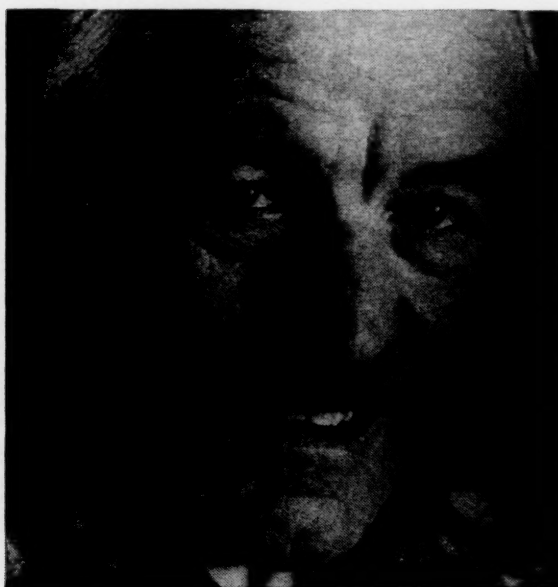
**RETIRED BUSINESSMAN**  
Easier on the Patient's Family



**GRANDMOTHER**  
Restored Emotional Balance



**SCHOOLTEACHER**  
Sense of Personal Freedom



**NEWSPAPERMAN**  
Occupational Continuity

# THE ORINASE EPOCH

## **BREAKTHROUGH FOR THE PATIENT**

A more normal, more secure life for the majority of diabetics.

## **BREAKTHROUGH FOR THE PHYSICIAN**

Smoother control, free from the danger of hypoglycemic shock.

## **BREAKTHROUGH FOR METABOLIC INVESTIGATORS**

New stimulus and new evidence in searching for the final answers to diabetes.

## ORINASE PRESCRIPTION INFORMATION

Dosage: Patients responsive to Orinase may begin therapy as follows:

First day ..... 3 Gm.

Second day ..... 2 Gm.

Third day ..... 1 Gm.

Usual maintenance dose ..... 1 Gm.

(must be adjusted to patient's response)

To change from insulin to Orinase:

If previous insulin dosage was

**less than 40 u./day**    reduce insulin 30% to 50% immediately; gradually reduce insulin dose if response to Orinase is observed.

**more than 40 u./day**    reduce insulin 20% immediately; carefully reduce insulin beyond this point if response to Orinase is observed. In these patients, hospitalization should be considered during the transition period.

Prior to using Orinase in selected patients, the physician should perform a complete physical examination and indicated laboratory studies. During the initial test period, the patient should report to the physician daily, and for the first month at least once weekly for physical examination and blood sugar determination. After the first month, the patient should be examined at monthly intervals or more frequently as indicated.

The patient should be instructed to report immediately to his physician if he does not feel as well as usual.

It is especially important that the patient, because of the simplicity and ease of administration of Orinase, does not develop a careless attitude ("cheating" on his diet, for example) which may result in serious consequences and failures of treatment.

**Supplied:** In 0.5 Gm. scored tablets, bottles of 50.

Complete literature available on request.

**Upjohn**

The Upjohn Company, Kalamazoo, Michigan

**ORINASE**



*Doctor*, do you feel that your colleagues are missing important new medical findings by not reading The American Journal of Medicine?

Let us send them a complimentary copy—of course there is no obligation to you or your colleagues. Just fill out the coupon and mail it to us.

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# The American Journal of Medicine

11 East 36th Street, New York 16, New York

Coming—November Issue

## Symposium on Nutrition in Internal Medicine

Guest Editor: DR. JOHN B. YOUMANS

1. Introduction

DR. JOHN B. YOUMANS  
Vanderbilt University School of Medicine  
Nashville, Tennessee

2. Nutrition in Internal Medicine

DR. R. H. KAMPMEIER  
Vanderbilt University School of Medicine  
Nashville, Tennessee

3. Diet in Liver Disease

DR. CHARLES S. DAVIDSON  
Thorndike Memorial Hospitals  
Boston, Massachusetts

4. Diet and Renal Disease

DR. ROBERT M. KARK  
University of Illinois, College of Medicine  
Chicago, Illinois

5. Diet and Metabolic Diseases (Diabetes especially)

DR. HERBERT POLLACK  
70 E. 77 Street  
New York, New York

6. The Physiologic Role of Vitamins

DR. WENDELL H. GRIFFITH  
University of California Medical Center  
Los Angeles, California

7. B-Vitamin Deficiencies

DR. W. M. SEBRELL, JR.  
Research Corporation  
New York, New York

8. Nutritional Anemias with Special  
Reference to Vitamin B<sub>12</sub>

DR. GRACE A. GOLDSMITH  
Tulane University School of Medicine  
New Orleans, Louisiana

9. Salt and Hypertensive Disease

DR. GEORGE E. MENEELY  
Vanderbilt University School of Medicine  
Nashville, Tennessee

10. How Much Is Enough

DR. W. J. DARBY  
Vanderbilt University School of Medicine  
Nashville, Tennessee

**THE AMERICAN JOURNAL OF MEDICINE**

**11 East 36th Street**

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to cope with cathartic habituation

## DORBANTYL®

(danthron + dioctyl sodium sulfosuccinate)

### PERISTALTIC STIMULANT + FECAL SOFTENER

In cathartic habituation, the action of DORBANTYL diminishes dependence on cathartics as it relieves constipation: "Careful attention to diet and fluid consumption, along with Danthron-D.S.S. [DORBANTYL] resulted in improved colonic motility. As bowel tone increased, gradual withdrawal of medication to complete discontinuance was possible in most instances."\*

*supplied:* DORBANTYL Capsules—Each containing danthron (DORBANE), 25 mg., and dioctyl sodium sulfosuccinate, 50 mg. Also available in double strength DORBANTYL Forte Capsules and as DORBANTYL Suspension.

\*Marks, M. M.: Clin. Med. 4:151, 1957.

### AND FOR GENTLE PERISTALTIC STIMULATION ALONE

## DORBANE®

(danthron)

For more rapid response or in occasional constipation prescribe crystalline-pure DORBANE, a gentle evacuant without cathartic griping.

*supplied:* Each DORBANE tablet or 2 teaspoonfuls of DORBANE Suspension contains 75 mg. danthron.

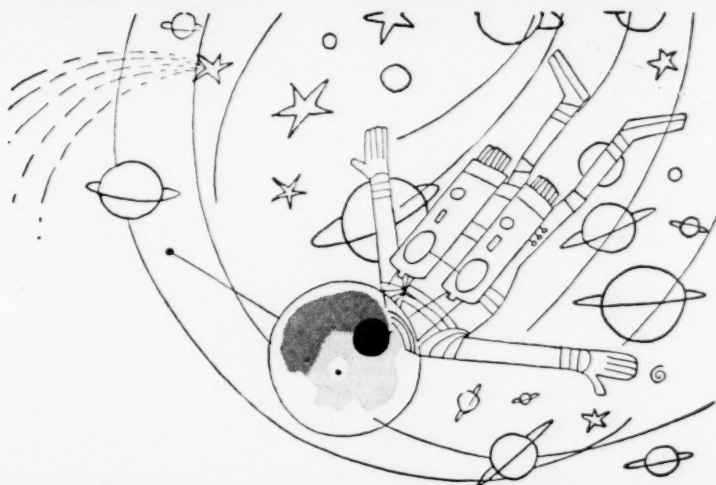
\*TRADEMARKS REG. U.S. PAT. OFF. DORBANTYL FORMULA PATENT PENDING.



**SCHENLABS PHARMACEUTICALS, INC.**  
NEW YORK 1, NEW YORK

Manufacturers of NEUTRAPEN® (penicillinase) for penicillin reactions.

53558



**BRING HIM BACK FROM OUTER SPACE**  
to feed the inner man



**REDISOL®**  
CYANOCOBALAMIN (CRYSTALLINE VITAMIN B<sub>12</sub>)

With REDISOL (vitamin B<sub>12</sub>)—new zest for meals. Soluble REDISOL tablets (25, 50, 100, 250 mcg.) and cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) mix readily with liquids.

REDISOL is a trade-mark of Merck & Co., Inc.



**MERCK SHARP & DOHME**

DIVISION OF MERCK & CO., Inc., PHILADELPHIA 1, PA.

## A Totally New Molecule

### for the Treatment of

- Chronic Fatigue States
- Mild Depression
- Chronic Headache
- Migraine
- Neurasthenia
- Behavior Problems and Learning Defects in Children

# Anti Depressant Deaner<sup>®</sup>

*p*-acetamidobenzoic acid salt of 2-dimethylaminoethanol

Extensive clinical trials in over 2,000 patients prove 'Deaner' to be of value in the alleviation of a wide variety of emotional disturbances. Patients who lack in energy, are mildly depressed, and find it difficult to concentrate are greatly benefited by 'Deaner'.

#### REPORTS FROM INVESTIGATORS

*In medical student volunteers, 'Deaner' produced increased daytime energy and attentiveness at lectures, sounder sleep (with a reduction in the hours of sleep needed), better ability to concentrate on both studying and writing, decreased apprehensiveness prior to and during examinations, a more affable mood and outspoken personality.*

1. Murphree, H. B., Jr.; Jenney, E. H., and Pfeiffer, C. C.: 2-Dimethylaminoethanol as a Central Nervous System Stimulant, Presented before Assoc. for Research in Nervous and Mental Disease, New York, Dec. 12-14, 1957. To be published.

*In Exhaustion and Depression—In a study of over 100 patients suffering from various psychiatric disorders, especially exhaustion and mild depression, the clinical effect of 'Deaner' was to increase energy and to relieve depression in over 70%.*

2. Lemere, F., and Lasater, J. H.: Am. J. Psychiat. 114:655 (Jan.) 1958.

*In Learning Problems—Some of the children with reading problems and other learning defects have improved markedly during their treatment with 'Deaner'.*

3. Oettinger, L., Jr.: Presented before the American Encephalographic Society Meeting, Atlantic City, June 14, 1958. To be published.

#### ADVANTAGES OF DEANER

Effects come on gradually and are prolonged...

*Without* causing hyperirritability, jitteriness or emotional tension...

*Without* causing excess motor activity...

*Without* causing loss of appetite...

*Without* elevating blood pressure or heart rate...

*Without* sudden letdown on discontinuance of therapy.

**DOSAGE:** Initially, 1 tablet (25 mg.) daily in the morning. Maintenance dose, 1 to 3 tablets; for children, ½ to 3 tablets. Full benefits may require two weeks or more of therapy. 'Deaner' is supplied in scored tablets containing 25 mg. of 2-dimethylaminoethanol.

Another *Riker* First

LOS ANGELES

*Unquestioned therapeutically  
...long established clinically*

# TRISEM

**SUSPENSION**

**(chocolate-flavored)**

For the many bacterial infections that respond promptly to triple sulfonamide therapy, Trisem presents a preferred formula.

Each 5 cc. contains, in a pleasant, chocolate-flavored vehicle:

Sulfamerazine (microcrystalline)	. . . . .	0.167 Gm. (2 3/5 gr.)
Sulfadiazine (microcrystalline)	. . . . .	0.167 Gm. (2 3/5 gr.)
Sulfamethazine (microcrystalline)	. . . . .	0.167 Gm. (2 3/5 gr.)

Each 5 cc. (1 tsp.) provides 0.5 Gm. total sulfonamides.

Each 15 cc. (1 tbsp.) provides 1.5 Gm. total sulfonamides.

## ADVANTAGES

- wide patient acceptability
- unquestioned therapeutic value
- high index of safety
- broad antibacterial spectrum
- provides high blood levels promptly
- economical for the patient

Many physicians prefer to use the sulfonamides to control bacterial infections because resistant organisms rarely develop. Nor, as with some broad spectrum therapy, is there the complication of such after-effects as moniliasis.

PACKAGING: In pint and gallon bottles.

**THE S. E. MASSENGILL COMPANY**

**BRISTOL, TENNESSEE**

**New York**

**Kansas City**

**San Francisco**



**Achromastatin\*V**



...THREATENED VITAMIN DEFICIENCY • PREVENT IT WITH

HIGH POTENCY VITAMIN-MINERAL SUPPLEMENT

# Achrostatin<sup>\*</sup>V

Lederle



...THREATENED VITAMIN DEFICIENCY • PREVENT IT WITH

# MYADEC

## HIGH POTENCY VITAMIN-MINERAL SUPPLEMENT

Each MYADEC Capsule provides the benefits of:

### *Vitamins:*

Vitamin B<sub>12</sub> crystalline ..... 5 mcg.  
 Vitamin B<sub>2</sub> (riboflavin) ..... 10 mg.  
 Vitamin B<sub>6</sub> (pyridoxine hydrochloride) 2 mg.  
 Vitamin B<sub>12</sub> mononitrate ..... 10 mg.  
 Nicotinamide (niacinamide) ..... 100 mg.  
 Vitamin C (ascorbic acid) ..... 150 mg.  
 Vitamin A ..... (7.5 mcg.) 25,000 units  
 Vitamin D ..... (25 mcg.) 1,000 units  
 Vitamin E ..... 5 I. U.  
 (d-alpha-tocopheryl-acetate concentrate)

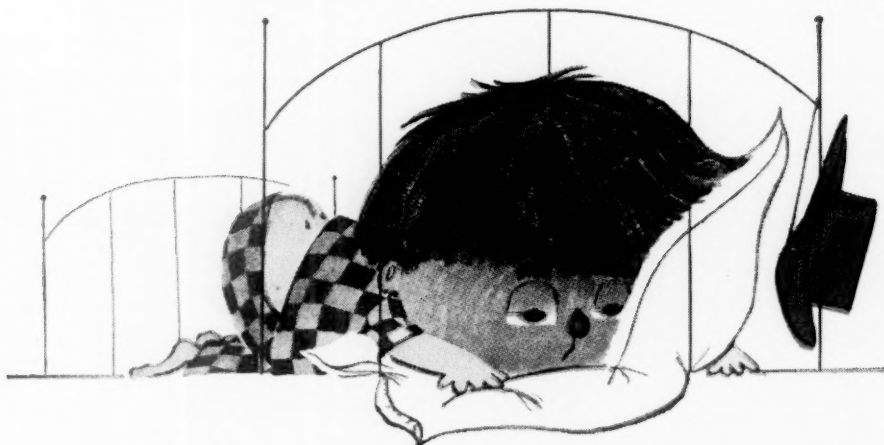
### *Minerals (as inorganic salts):*

Iodine ..... 0.15 mg.  
 Manganese ..... 1.0 mg.  
 Cobalt ..... 0.1 mg.  
 Potassium ..... 5.0 mg.  
 Molybdenum ..... 0.2 mg.  
 Iron ..... 15.0 mg.  
 Copper ..... 1.0 mg.  
 Zinc ..... 1.5 mg.  
 Magnesium ..... 6.0 mg.  
 Calcium ..... 105.0 mg.  
 Phosphorus ..... 80.0 mg.  
 Bottles of 30, 100, 250, and 1,000.



PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

When fever and aches  
have little "Tyler"  
corralled...



# Tylenol<sup>®</sup>

ELIXIR/DROPS

...pediatric antipyretic-analgesic...

**gets him back on the trail**

Tylenol rides hard on pain and fever... makes childhood illnesses easier to bear for both youngsters and mothers.

The *first* pediatric dosage form of acetaminophen, Tylenol reduces fever and relieves pain quickly, safely and without upsetting queasy young stomachs. Children like the cherry flavor of Tylenol Elixir... and Tylenol Drops make administration easy even for infants.

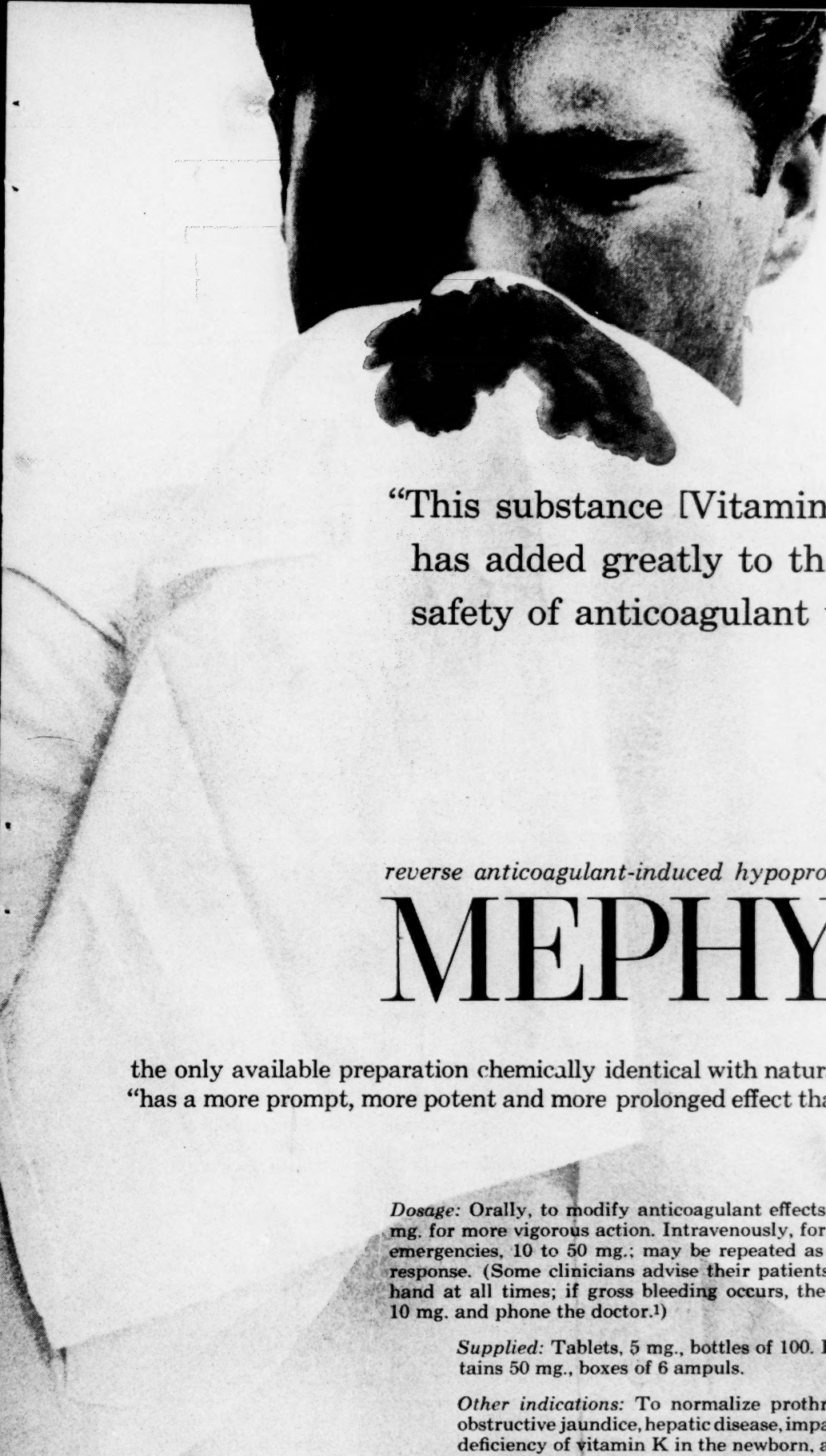
Copyright, McNeil Laboratories, Inc.

*for simplified administration for all children...*

**Rx Tylenol Elixir** — 120 mg. (2 gr.) per 5 cc.; bottles of 4 and 12 fl. oz.  
**Tylenol Drops** — 60 mg. (1 gr.) per 0.6 cc.; 15 cc. bottles with calibrated plastic dropper.

**McNEIL**

LABORATORIES, INC.  
PHILADELPHIA 32, PA.



"This substance [Vitamin K<sub>1</sub>]  
has added greatly to the  
safety of anticoagulant therapy"<sup>1</sup>

*reverse anticoagulant-induced hypoprothrombinemia*

# MEPHYTON<sup>®</sup>

VITAMIN K<sub>1</sub>

the only available preparation chemically identical with naturally-occurring vitamin K<sub>1</sub>...  
"has a more prompt, more potent and more prolonged effect than the vitamin K analogues"<sup>2</sup>

**Dosage:** Orally, to modify anticoagulant effects: 5 to 10 mg. initially; 15 to 25 mg. for more vigorous action. Intravenously, for anticoagulant-induced bleeding emergencies, 10 to 50 mg.; may be repeated as indicated by prothrombin time response. (Some clinicians advise their patients to keep a supply of tablets on hand at all times; if gross bleeding occurs, the patients are instructed to take 10 mg. and phone the doctor.<sup>1</sup>)

**Supplied:** Tablets, 5 mg., bottles of 100. Emulsion, each 1-cc. ampul contains 50 mg., boxes of 6 ampuls.

**Other indications:** To normalize prothrombin time—before surgery, in obstructive jaundice, hepatic disease, impaired gastrointestinal absorption, deficiency of vitamin K in the newborn, and following the administration of antibiotics, sulfonamides, and salicylates. 'Mephyton' is a valuable addition to the physician's bag for emergency use.



**MERCK SHARP & DOHME**

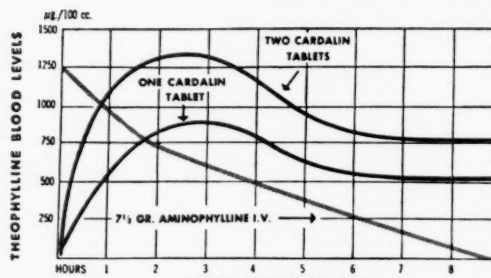
DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

Mephyton is a trade-mark of MERCK & CO., INC.

1. Wright, I. S.: Early use of anticoagulants in treatment of myocardial infarction, J.A.M.A. 163: 918-921, March 16, 1957.  
2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.

A NEISLER RESEARCH PRODUCT

higher and  
more sustained  
theophylline  
blood levels ...  
orally



(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11:301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100:309, 1950.)

# CARDALIN

proven effective clinically whenever high blood levels of theophylline are desired. Cardalin contains two protective factors\* to guard against the nausea, gastric irritation and vomiting which occasionally accompany a high oral dose of aminophylline.

\*U. S. Patent No. 2,667,439

Each tablet contains:

Aminophylline..... 5.0 gr.  
Aluminum hydroxide..... 2.5 gr.  
Ethyl aminobenzoate..... 0.5 gr.  
Also available as Cardalin-Phen with 1/4 gr. phenobarbital.

To serve your patients today—call your pharmacist for any additional information you may need to prescribe Cardalin. And for prescription economy, prescribe Cardalin in 50's.

Irwin, Neisler & Co. • Decatur, Illinois

**Neisler**



*Psoriasis can destroy the most beautiful body in the world ...*

**LIPAN** capsules added  
to your armamentarium will provide...

maximum effect with minimum inconvenience to the patient. No messy ointments or lotions. When following your prescribed regimen an impressive percentage of patients will become free of the symptoms.

**LIPANIZE THE PSORIATIC**

**TO OBTAIN SYMPTOM-FREE PATIENTS**

Complete LIPANIZATION of the patient is essential for successful clinical results. LIPANIZATION is accomplished with saturation doses of LIPAN and produces a gradual reduction of the hypercholesteremia and hyperlipemia usually present in the psoriatic.

**Dosage:** Initial administration of LIPAN requires twelve (12) to fifteen (15) capsules daily in conjunction with food intake. After complete LIPANIZATION which requires about ten days, dosage is then adjusted to the quantity of food ingested.

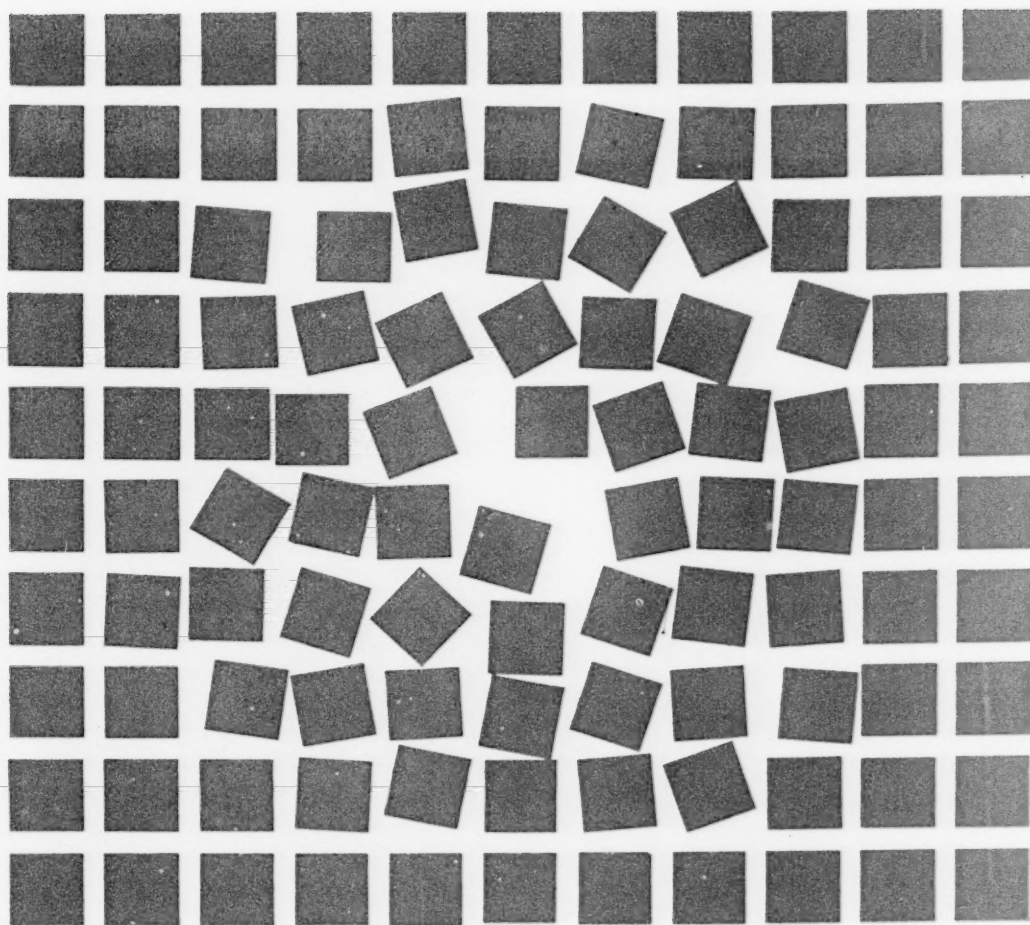
**Maintenance Dosage:** After complete remission of lesions the dose is usually one (1) to two (2) capsules with each intake of food.



LIPAN Capsules or Tablets contain: Specially prepared highly activated, desiccated and defatted whole Pancreas. Thiamin HCl, 1.5 mg. Vitamin D, 500 I.U.

Available: Bottles 180's, 500's

Samples Literature upon request **Spiert & Co., Inc.** Waterbury, Conn.



## RATIONAL ADJUNCT TO ANTIBIOTIC THERAPY

Current opinion stresses the desirability of supportive measures in the antibiotic treatment of severe infections.<sup>1,2</sup> In addition to protein, calories and electrolytes, the adjunct use of STRESSCAPS speeds recovery by replenishing the specific water-soluble vitamin losses sustained by patients in stressful states.

1. Pratt, R.: *Geriatrics* 11:341 (June) 1957. 2. Pulaski, E.J.: *Antibiotics Annual* 1953-1954, Proceedings of the Symposium on Antibiotics Sponsored by U. S. Department of Health, Education and Welfare, Food and Drug Administration, Division of Antibiotics, 1953, Medical Encyclopedia, Inc., New York, p. 227.

### Each Capsule Contains:

Thiamine Mononitrate (B <sub>1</sub> )	10 mg.
Riboflavin (B <sub>2</sub> )	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B <sub>6</sub> )	2 mg.
Vitamin B <sub>12</sub>	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.

Average Dose: 1-2 capsules daily.

# STRESSCAPS<sup>\*</sup>

STRESS FORMULA VITAMINS LEDERLE

### STRESSCAPS IN STRESS:

- Infection
- Physiologic Trauma
- Endocrine Dysfunction
- Emotional Stress
- Pre- and Postoperatively



LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

\*Reg. U.S. Pat. Off.

## A Summary Report on CORTROPHIN<sup>®</sup>-ZINC

(Corticotropin-Alpha Zinc Hydroxide)

**Description:** A unique patented electrolytic process (developed by Organon research) produces a complex of *alpha* zinc hydroxide and corticotropin. This complex offers considerable advantages for practical ACTH therapy.

**Characteristics:** New Cortrophin-Zinc provides corticotropin of unsurpassed purity with low foreign protein content. This reduces the risk of sensitization reactions.

Since about 5% of the corticotropin is uncombined, onset of clinical response is rapid. But the balance, present as a complex of alpha zinc hydroxide, provides a prolonged action so that the effective time span of a single dose is usually several days. Injection of the new electrolytic Cortrophin-Zinc is virtually painless.

**Pharmacology:** A potent stimulator of cortical activity, Cortrophin-Zinc *does not depress* functioning of the suprarenal glands. Unlike the corticosteroids, adrenocorticotrophic hormone arouses the adrenal glands to produce *natural* steroids in natural proportions. In a 5-year study of patients on ACTH therapy, no case of adrenal *or* pituitary depression or atrophy has been observed. Because Cortrophin-Zinc is virtually painless on injection and its prolonged action obviates frequent injections, it is now practicable to use Cortrophin-Zinc in most of the indications where formerly reliance has been on corticosteroids. This freedom from apprehen-

sion of deleterious depressive effects permits clinical use of valuable hormone therapy on a broader scale than has been possible heretofore.

**Clinical Uses and Dosage:** The many published reports on the use of Cortrophin-Zinc as well as ACTH, in thousands of patients indicate its value in over 100 disorders. Most responsive have been: allergies and hypersensitivities, rheumatoid arthritis, bronchial asthma, serum sickness and inflammatory skin and eye diseases.

Dosage should be individualized, but generally initial control of symptoms is obtained with a single injection of 40 units of Cortrophin-Zinc daily, until control is evident. Maintenance dosage is generally 20 units (or less) twice a week.

Use of Cortrophin-Zinc with oral steroids is now recommended as a safety measure to supply the important suprarenal stimulation and lessen the hazard of atrophy. Periodic use of Cortrophin-Zinc is advocated with all steroid analogs, such as cortisone, hydrocortisone, prednisone, prednisolone, methylprednisone, and triamcinolone.\*

**Supply:** 5-cc vials containing 40 and 20 U.S.P. units of corticotropin per cc; 1-cc ampuls containing 40 and 20 U.S.P. units of corticotropin, with sterile disposable syringes.

\*Write for complete literature and bibliography containing specific dosage schedules to:

*Medical Department*

ORGANON INC. • Orange, N. J.



## Doctors, too, like "Premarin"®

**T**HE doctor's room in the hospital is used for a variety of reasons. Most any morning, you will find the internist talking with the surgeon, the resident discussing a case with the gynecologist, or the pediatrician in for a cigarette. It's sort of a club, this room, and it's a good place to get the low-down on "Premarin" therapy.

If you listen, you'll learn not only that doctors like "Premarin," but *why* they like it.

The reasons are simple. Doctors like "Premarin," in the first place, because it really relieves the

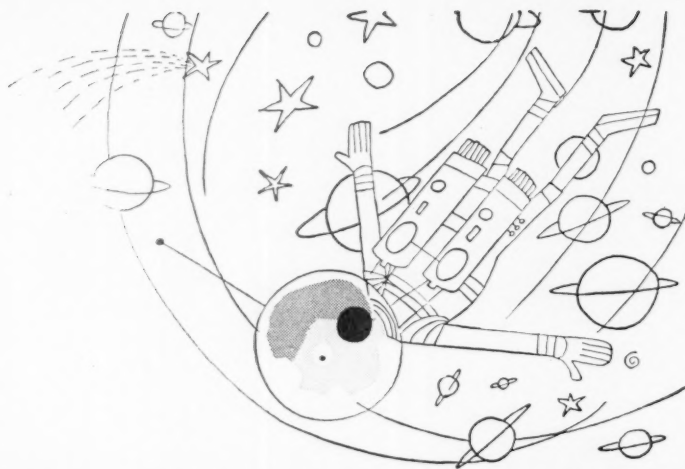
symptoms of the menopause. It doesn't just mask them — it replaces what the patient lacks — natural estrogen. Furthermore, if the patient is suffering from headache, insomnia, and arthritic-like symptoms due to estrogen deficiency, "Premarin" takes care of that, too.

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**T**HERAPY for the menopause syndrome should relieve not only the psychic instability attendant the condition, but the vasomotor instability of estrogen decline as well. Though they would have a hard time explaining it in such medical terms, this is the reason women like "Premarin."

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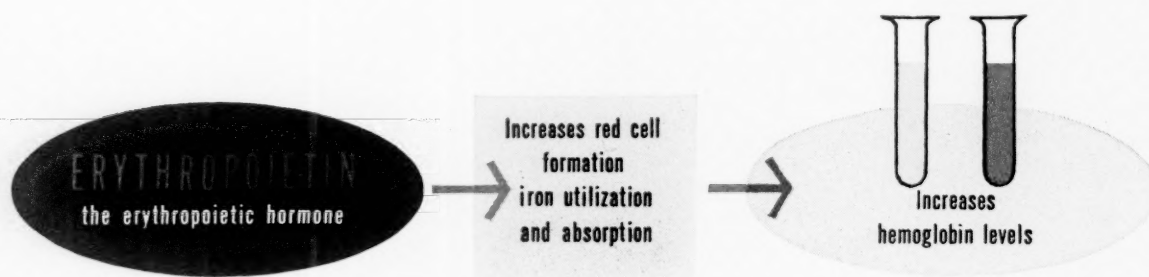
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## LUNG ABSCESS

### KANTREX Clinical Report No. 744 "EXCELLENT" RESPONSE TO KANTREX AFTER OTHER ANTIBIOTICS FAIL

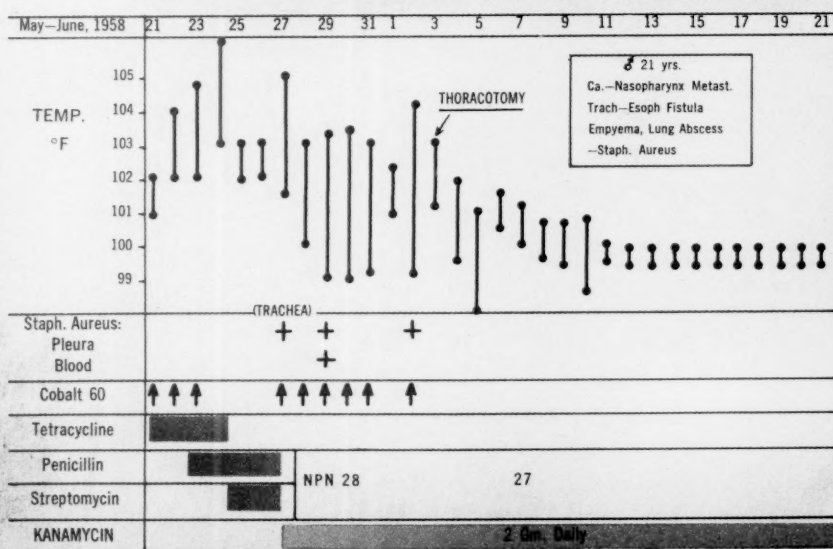
E. T., a 21-year-old male with mediastinal and pulmonary carcinoma presumed to have arisen from the nasopharynx, developed a lung abscess and empyema due to a drug-resistant staphylococcus of phage type 47/53/54/VA, while receiving treatment with Cobalt 60.

The patient was first treated with tetracycline, penicillin, and streptomycin, but became worse. He was started on KANTREX in a dosage of 0.5 Gm. q.i.d. Of interest was the finding that the empyema fluid contained 5.5 mcg./ml. and the blood serum 5.2 mcg./ml. of KANTREX 4 hours after the fifth dose.

Although defervescence did not occur immediately, the patient seemed to improve during a 7-day period in association with aspirations of his empyema cavity. Then it was elected to do a thoracotomy and establish underwater drainage. Following this procedure, improvement was rapid.

During treatment with KANTREX, a tracheo-esophageal fistula developed, but despite this, the patient became asymptomatic and virtually afebrile. The fistula subsequently healed on KANTREX therapy.

White, A., and Knight, V., School of Medicine, Vanderbilt University, Nashville, Tenn.: *Annals New York Acad. Sci.* (In press).



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by investigators*

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*KANTREX Capsules are intended solely for intestinal antisepsis and the treatment of intestinal infections.*

*The Intramuscular form should be used for systemic infections.*

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KANTREX Intramuscular is available for systemic use in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX (kanamycin sulfate) 0.5 Gm. in 2 ml. volume.  
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Some of the 85 eminent investigators who reported on KANTREX at the Conference sponsored by the New York Academy of Sciences:

1. Berman, L., and Katz, S.: Georgetown University School of Medicine, Washington, D.C.
2. Bunn, P., Baltch, A., and Krajnyak, O.: State University of New York Upstate Medical School, Syracuse, N. Y.
3. Chalmers, G. C., Sebestyen, K., and Timberlake, W. H.: Harvard Medical School and Tufts University School of Medicine, Boston, Mass.
4. Cohn, I., Jr.: Louisiana State University School of Medicine, New Orleans, La.
5. Cronk, G. A., and Naumann, D. E.: Dept. of Health and Preventive Medicine, Syracuse University, Syracuse, N. Y.
6. Davies, F. G.: Marcy State Hospital, Marcy, N. Y.
7. Finegold, S. M., Winfield, M. E., Aronsohn, R. B., Hewitt, W. L., and Guze, L. B.: University of California Medical School, Los Angeles, Calif.
8. Finland, M.: Harvard Medical School, Boston, Mass.
9. Greey, P. H., and Wightman, K. J. R.: University of Toronto, Toronto, Can.
10. Herrold, R. D., and Karabatsos, N.: College of Medicine, University of Illinois, Chicago.
11. Hewitt, W. L., and Finegold, S. M.: University of California School of Medicine, Los Angeles, Calif.
12. High, R. H., Sarria, A., and Huang, N. N.: Temple University School of Medicine, Philadelphia, Pa.
13. Prigot, A., Shidlovsky, B. A., and Campbell, E. A.: Department of Hospitals, New York City.
14. Rutenberg, A. M., Koota, G. M., and Schweinburg, F. B.: Harvard Medical School, Boston, Mass.
15. Thurman, W. G., and Platou, R. V.: Tulane University School of Medicine, New Orleans, La.
16. Welch, H., Wright, W. W., Weinstein, H. I., and Staffa, A. W.: Dept. of Health, Education and Welfare, Food and Drug Administration, Washington, D.C.
17. White, A., and Knight, V.: School of Medicine, Vanderbilt University, Nashville, Tenn.
18. Yow, E. M., and Monzon, O. T.: Baylor University College of Medicine, Houston, Tex.
19. Yow, M. D., and Womack, G. K.: Baylor University College of Medicine, Houston, Tex.

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# K?

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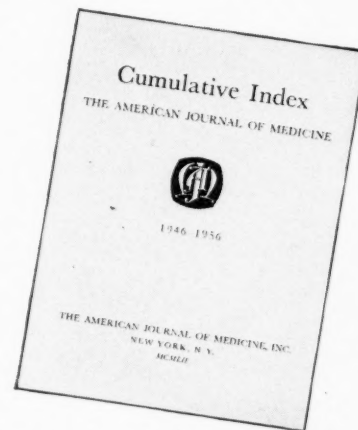
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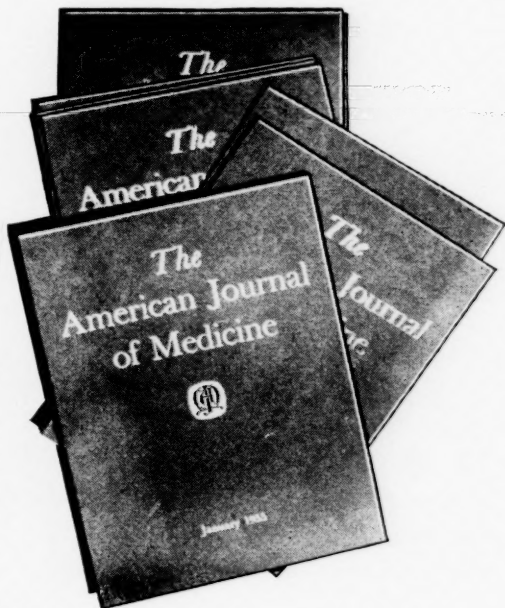
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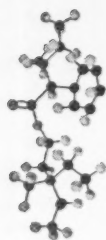
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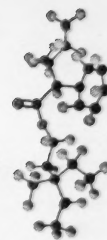
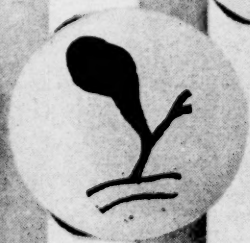
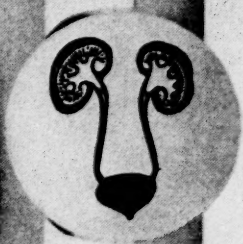
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Peiser<sup>2</sup> states that even extremely strong convulsive abdominal pain and violent vomiting could be eliminated or substantially improved, and no unpleasant side effects or toxic reactions were noted at any time.

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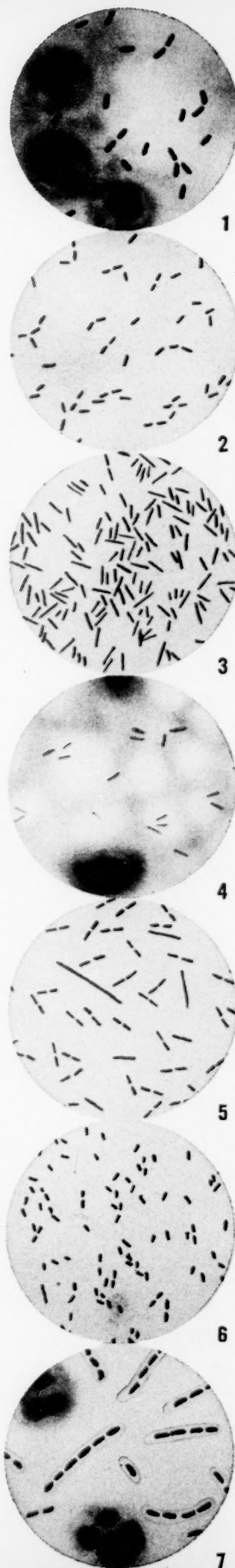
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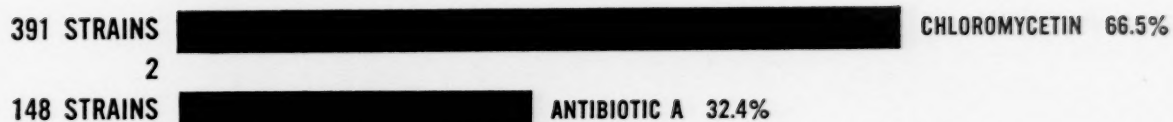


# IN VITRO SENSITIVITY OF SEVEN GRAM-NEGATIVE PATHOGENS TO CHLOROMYCETIN AND TO ANOTHER WIDELY USED ANTIBIOTIC\*

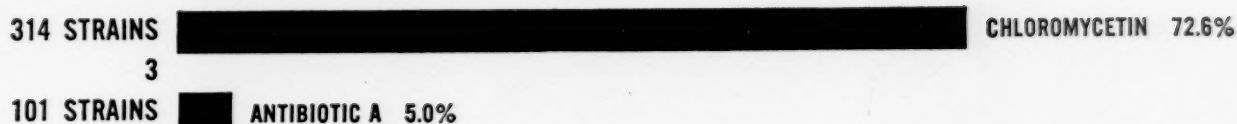
## ESCHERICHIA COLI



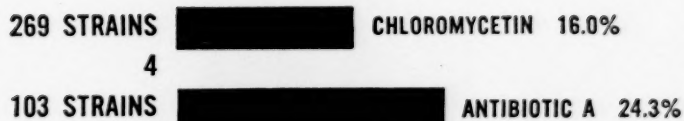
## AEROBACTER AEROGENES



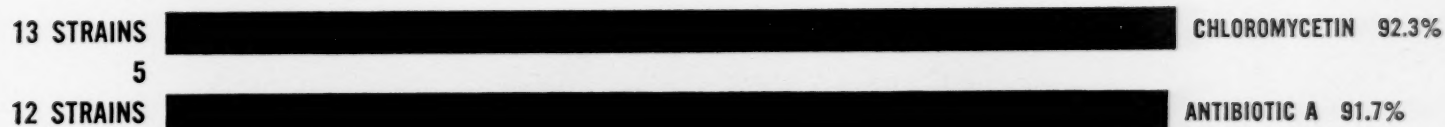
## BACILLUS PROTEUS



## B. PYOCYANEUS



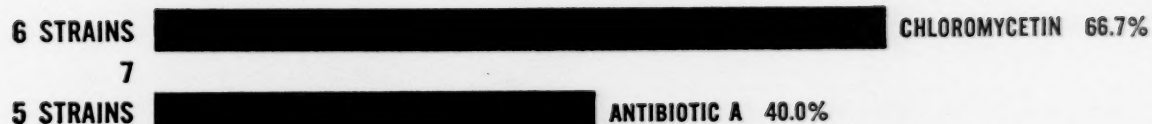
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## B. FRIEDLANDER



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\*Adapted from Schneierson.<sup>1</sup>

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both cause and fear of

# ANGINA

# ATTACKS

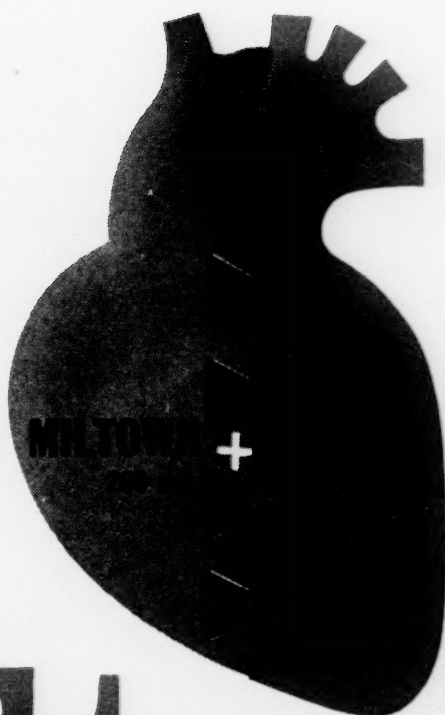
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1. Friedlander, H. S.: The role of ataraxics in cardiology. *Am. J. Card.* 1:395, March 1958.

2. Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. *Angiology* 8:504, Dec. 1957

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NEUTRAPEN is well tolerated when used intramuscularly and “...virtually nontoxic [pharmacologically], even at dose levels several hundred times the minimum effective dose.”<sup>7,2</sup>

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**Therapeutic:** NEUTRAPEN is indicated for the treatment of the allergic reactions to penicillin, such as urticaria,

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**Diagnostic:** Zimmerman suggests that “...response [to NEUTRAPEN] may be considered a useful tool in the differential diagnosis of eruptions where penicillin is only one of several possible inciting allergens.”<sup>3</sup>

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**supplied** NEUTRAPEN is supplied in single-dose vials containing 800,000 units of purified injectable penicillinase as lyophilized powder. It is stable at room temperature in the dry state.

**references:** (1) Becker, R. M.: *New England J. Med.* 254:952, 1956. (2) Chen, J. Y. P.; Bard, J. W., and Balsito, A. A., in Welch, H., and Marti-Ibanez, E.: *Antibiotics Annual 1957-1958*, New York, Medical Encyclopedia, Inc., 1958, p. 321. (3) Zimmerman, M. C., in Welch, H., and Marti-Ibanez, E.: *Antibiotics Annual 1957-1958*, New York, Medical Encyclopedia, Inc., 1958, p. 312. (4) Becker, R. M.: *A New Concept in Treatment of Penicillin Reactions—Use of Penicillinase*, paper presented at 106th Ann. Meet., A.M.A., New York, N. Y., June 3-7, 1957. (5) Becker, R. M., in Welch, H., and Marti-Ibanez, E.: *Antibiotics Annual 1957-1958*, New York, Medical Encyclopedia, Inc., 1958, p. 310. (6) Minno, A. M., and Davis, G. M.: *J.A.M.A.* 165:222, 1957. (7) Davis, G. M.: *Discussion, Antibiotics Symposium*, Washington, D. C., October 3, 1957. (8) Zimmerman, M. C.: *Clin. Med.* 5:305, 1958.

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\*Diagnex Blue has been used in thousands of gastric analyses with conclusive evidence of accurate results (95% accurate identification of acid secretors, 97% accuracy in identifying achlorhydrics).

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Start test immediately on arising, without eating or drinking anything for breakfast.

			
<b>START</b>	Urinate. Do not keep this urine.	Tear open the small packet and swallow the 2 tablets with a glass of water.	
			
<b>1 HR. LATER</b>	Urinate. Save urine in jar marked "control urine".	Open large packet. Pour con- tents into 1/4 glass of water.	Stir well and drink it. (The granules do not dissolve.) If granules remain, add a little more water and drink them down.
			
<b>2 HRS. LATER</b>	Urinate. Save urine in jar marked "test urine".		

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Each box of DIAGNEX BLUE has a color comparator block with two color standards—one representing color intensity of 0.6 mg. azure A, and the other 0.3 mg. azure A. Color comparison should be made against a suitable light source.

- A. 1. Dilute the control and test urines with water to 300 cc. each.
  2. Fill two test tubes with approximately 10 cc. of control urine each, and fill a third test tube with about 10 cc. of the test urine.
  3. Place the test urine tube in the middle slot of the comparator and the control urine tubes in front of the two color standards.
  4. If the color intensity of the test urine is equal to or exceeds that of the 0.6 mg. standard, the patient has secreted free gastric hydrochloric acid and the test is complete.
- B. 1. If the test sample color is less intense in color

than the 0.6 mg. standard, acidify all samples with 2 drops of diluted (10%) hydrochloric acid. Heat the three test tubes in a boiling bath for 10 minutes. (Boiling may decolor sample, but color will reappear on cooling.) Remove tubes from the bath and allow to cool for 2 hours. Compare color intensity as in A3 and A4.

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Council on Drugs, New and Nonofficial Remedies:  
Philadelphia, J. B. Lippincott Co., 1958, p. 285.

Now, concomitant use of a newly discovered antihypertensive agent ['Diuril' (Chlorothiazide)] has been found to enhance the hypotensive effect of 'Inversine'—while reducing the required dosage of 'Inversine' and often minimizing the serious side effects of ganglionic blockade.

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- usefulness not limited by development of tolerance
- it has a gradual onset of effect, reducing the likelihood of sudden drops in blood pressure

**'Diuril'**

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*new and unique  
antihypertensive agent*

- provides basic therapy to improve and simplify the management of hypertension
- markedly enhances the effects of other antihypertensive agents
- often reduces dosage requirement of ganglionic blocking agents and other antihypertensive agents below the level of serious side effects
- smooths out blood pressure fluctuations
- added to other antihypertensive agents, is often effective in controlling blood pressure of even highly resistant cases
- effectiveness not diminished by development of tolerance
- well tolerated even at maximum therapeutic doses

**DOSAGE RECOMMENDATIONS****New Patients***1. Initiate therapy with 'Diuril'*

'Diuril' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

*2. Adjust dosage of other agents*

The dosage of other antihypertensive medication ('Inversine', reserpine, veratrum, hydralazine, etc.) is adjusted as indicated by patient response.

'Inversine' is given in the same manner whether used with 'Diuril' or alone. Recommended initial dosage is 2.5 mg. twice a day, preferably after meals. May be increased

by 2.5 mg. at intervals of no less than two days until desired response is obtained. In severe or urgent cases, the increments may have to be larger or more frequent, with the largest dose given preferably at noon or in the evening. 'Inversine' is extremely potent and should always be titrated according to the patient's orthostatic blood pressure response.

*3. Adjust dosage of all medication*

The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

**Patients on 'Inversine' and/or other ganglionic blocking agents***1. Initiate therapy with 'Diuril'*

'Diuril' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

*2. Adjust dosage of ganglionic blocking agent*

If the patient is established on a ganglionic blocking agent (e.g., 'Inversine') it should be continued, but the total daily dosage should *immediately* be reduced by as much as 25 to

50 per cent. This will reduce the serious side effects often observed with ganglionic blockade.

*If other antihypertensive agents are used, their dosage should be adjusted as indicated by patient response.*

*3. Adjust dosage of all medication*

The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

**Precautions:** Side effects of 'Inversine' are essentially the same as those encountered with other ganglionic blocking agents. At the first sign of constipation, vigorous treatment must be initiated immediately since paralytic ileus may result if constipation is unchecked. Patients should be informed how to cope with postural hypotension should this occur. 'Inversine' is contraindicated in coronary insufficiency, organic pyloric stenosis and recent myocardial infarction.

**Supplied:** 'Inversine' tablets of 2.5 mg. and 10 mg. Bottles of 100. 'Diuril' tablets of 250 mg. and 500 mg. Bottles of 100 and 1000.

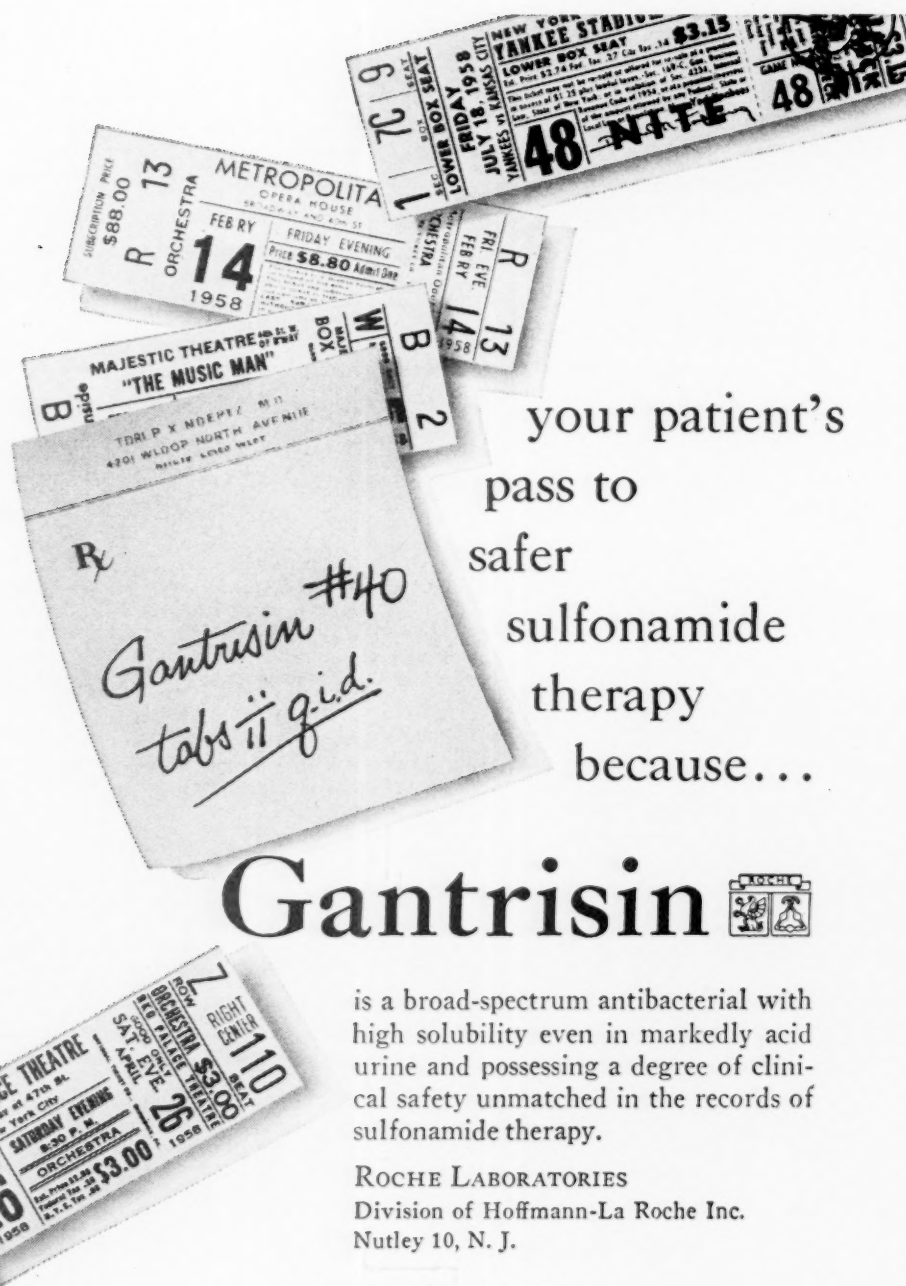
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*Documentary Case History . . .*

# Hypertension controlled for four years with **Serpasil**<sup>®</sup> (reserpine CIBA)

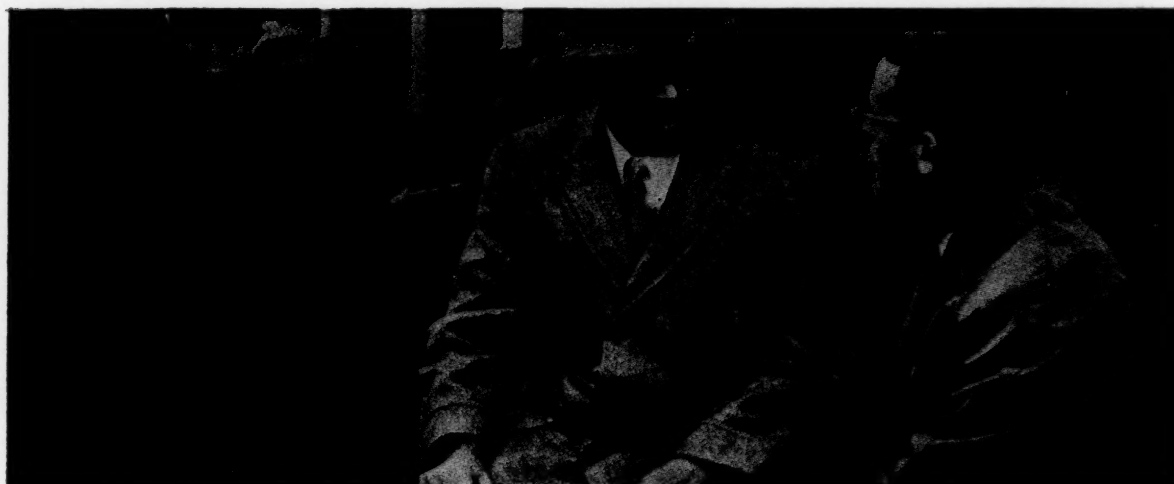


K. C., a 67-year-old retired shirt manufacturer, had a 16-year history of hypertension, was troubled by recurrent dizzy spells and headaches. "I'd get several attacks a day. . . . Usually I'd go into the bedroom and lie down." Serpasil therapy was started four years ago, effecting a gradual reduction of the patient's initial blood pressure of 220/120 mm. to the present 140/80. Now well and asymptomatic, ". . . I'm able to go to matinees and see some of the TV shows."

**SUPPLIED:** TABLETS, 4 mg. (scored), 2 mg. (scored), 1 mg. (scored), 0.25 mg. (scored) and 0.1 mg.

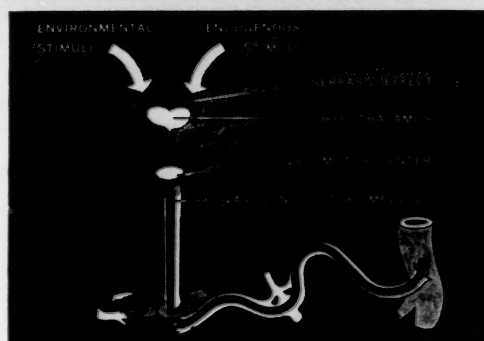
**ELIXIRS,** 1 mg. and 0.2 mg. Serpasil per 4-ml. teaspoon.

**PARENTERAL SOLUTION:** *Ampuls*, 2 ml., 2.5 mg. Serpasil per ml. *Multiple-dose Vials*, 10 ml., 2.5 mg. Serpasil per ml.



## *Hypertension controlled through* **SYMPATHETIC REGULATION**

Serpasil shields the psychic and somatic reaction centers from emotional and environmental stress stimuli, thereby inhibiting the discharge of vasoconstrictive impulses through the sympathetic nerves.



**C I B A** SUMMIT, N. J.

2/2535HK

Adapted from Moyer, J. H., Dennis, E., and Ford, R.: Arch. Int. Med. 96:530 (Oct.) 1955.

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Percentage reduction of excess serum cholesterol (over 150 mg. percent)	Percentage of patients experiencing various degrees of decline in excess serum cholesterol
Less than 20%	12.5%
20-40%	55 %
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'Cytellin' provides the most rational and practical therapy available. Without any dietary adjustments, it lowers elevated serum cholesterol concentrations in most patients.

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reduction of excess serum cholesterol (over 150 mg. percent) has been experienced.

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*May we send more complete information and bibliography?*

\*'Cytellin' (Sitosterols, Lilly)

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

873009

# The American Journal of Medicine

VOL. XXV

SEPTEMBER, 1958

No. 3

## Editorial

### Hunger and Appetite

#### *Physiologic Regulation of Food Intake*

IT is a commonplace that healthy men and animals maintain their weight with remarkable consistency over long periods of time. They adjust food intake to energy requirements with such precision that body stores of fat vary only slightly. This is the most easily appreciated evidence of a physiologic mechanism which regulates caloric intake. Such a regulatory device must be both complex and subtle in operation since it integrates information derived from the volume of each meal, the number of meals eaten daily, and the nutritive density of the mixed diet consumed. It is not surprising, therefore, that only an incomplete account can be given at present of the nature of this device. But, with the realization that the problem of hunger and appetite is one of regulation rather than of sensation, a better understanding of the processes involved has been gained in the last decade.

*Definitions.* Traditional usage of the terms *hunger* and *appetite* as sensations has been so varied that many have advocated their banishment for the sake of linguistic peace. Their stubborn longevity appears to this observer to mean that there is some basis of reality for the distinction drawn between hunger and appetite in every day speech. However, physiologic problems will not be solved by the dictionary. The only justification for presenting definitions advanced before [7] is that others in this field have found them of some (limited) use. *Hunger* is the physiologic state resulting from deficits of

nutrients which manifests itself in a disagreeable complex of sensations including the epigastric hunger pang, and behavioristically in activated feeding reflexes and increased motor activity. *Appetite* on the other hand may be defined simply as the desire for food, and is a matter of affect. As such its opposite is *satiety*, lack of the desire to eat or absence of the desire to eat which is associated with repletion of the nutrient deficits. It is clearly different from *anorexia*, in which the physiologic state of hunger is present without the desire to eat.

It is the task of physiological psychology to establish the way in which deficits in nutrients lead to alteration in psychic states, and numerous investigators have devoted themselves to this problem. But whether or not caloric deficits overflow into consciousness, there remains a "hard core" of physiologic regulation with which the present account is concerned.

#### PHYSIOLOGIC REGULATION

There is some question as to what is being regulated in relation to food intake. For some investigators it is energy intake in relation to energy output [2]. For others it is body weight *per se*. For yet others it is the body's store of nutrients [4,5]; since the total quantity of carbohydrate stored as glycogen ordinarily is small, at most some 75 gm. in man, this storage of nutrients is largely in the form of depot fat. Finally, combinations of these concepts have been suggested: For example that it is the re-

lationship of energy intake to energy output which is being regulated on a day-to-day basis, and that it is the body weight (energy stores) which is being regulated on a long term basis [6]. Brobeck has argued that food intake, heat loss and exercise are regulated directly, and that body weight is "controlled indirectly through regulation of the other three variables" [7]. For him it is energy exchange between the animal and its environment that is being regulated.

Under standard conditions there are marked variations in the day-to-day food intake in many species including man [8]. Our own experiments on intragastric feeding in the dog indicate that weeks are required to adjust intake to varied caloric deficits or excesses [9]. I therefore favor the view that what is being regulated or corrected in the long run is the body's store (excesses or deficits) of nutritional elements.

*The Neural Basis of Regulation.* The taking of food is a complex act of behavior under the control of the nervous system. Brobeck and his colleagues have established the importance of two areas in the hypothalamus for this activity [10]. Three observations are fundamental: (1) Lesions of the hypothalamus at the level of the ventromedial nucleus induce obesity by increasing food intake. (2) Lesions of the lateral area at this level of the hypothalamus abolish or markedly diminish food intake. (3) Destruction of both these areas results in a failure of feeding. Since there are separate mechanisms for starting and stopping eating, the medial mechanism has been identified with the "satiety center" and the lateral area with the "appetite center."

In Brobeck's analysis [11] the function of these hypothalamic centers is either to inhibit or to facilitate certain "feeding reflexes" which include visual, auditory, olfactory, tactile, gustatory and enteroceptive reflexes as well as reflexes of attention, approach, examination, ingestion (including chewing and swallowing) and rejection. The finding that destruction of both lateral and medial areas of the hypothalamus results in a failure of feeding suggests that the medial mechanism inhibits the lateral mechanism, but there is other evidence that these centers act upon lower areas in the brain stem and cord. Although chewing and swallowing occur in decerebrate animals, and the anencephalic infant feeds, the other reflexes cited require participation of the cerebral cortex. It would therefore appear that the regulatory system projects beyond the area of the hypothalamus.

#### CONTROL OF THE CENTRAL REGULATORY MECHANISM

Current research on the factors which govern the activity of the central regulatory mechanism has been concerned mainly with changes occurring within the organism after food has been eaten, which directly or indirectly affect the hypothalamus. The search has been for signals which suppress the activity of the lateral hypothalamus and stimulate the medial hypothalamus. The emphasis has been on the mechanism by which animals and men avoid overeating. These factors fall into two main groups: (1) the gastrointestinal consequences of food ingestion, and (2) the metabolic consequences of food absorption and assimilation.

*Gastrointestinal Aspects of Regulation.* In Cannon's account of hunger, the gastric hunger contractions give rise to the characteristic sensation of hunger, the epigastric pang [12]. The studies of Grossman and Stein [13] on insulin-induced hunger sensations before and after gastric denervation by vagotomy or sympathectomy indicate that the epigastric pang is only one (and a dispensable) component of the entire complex of hunger sensations. But even if the gastric hunger contractions are cues for stimulating food intake in some individuals (and evidence indicates that these are in the minority) the classic account does not assign any controlling role to this phenomenon.

There is, however, evidence that the upper gastrointestinal tract does have a regulatory function in metering the amount of food eaten on a meal-to-meal basis. (1) In the dog, prefeeding of a portion of the regular diet shortly before *ad lib* feeding reduces intake by a corresponding amount. (2) Sham feeding induces a short-lived satiety [14]. It appears that stimulation of oropharyngeal receptors associated with tasting, chewing and swallowing food contribute to controlling the amount of food ingested by inducing temporary satiety. This oropharyngeal metering of the volume of food eaten may act through proprioceptive impulses, perhaps from the jaws. It would not be too facetious to refer to this as the "work of eating."

A more important factor in regulating intake is gastric distention. It has been shown that sham feeding in dogs that had undergone esophagostomy is inhibited by gastric distention induced by calorically inert materials or a balloon. Similar results occurred in dogs with gastric fistulas in which prolonged distention induced a sustained depression of food [14,15].

Metering by gastric distention is probably mediated by vagal afferent fibers arising from the gastric stretch receptors recently described by Paintal [16]. These stretch receptors also govern the effects of volume on the rate of emptying of the stomach. Hunt has recorded the striking fact that during the central part of the digestive period the rate of outflow from the stomach with a large meal is actually less than with small meals [17]. This further reinforces the inhibitory effect of the volume of food ingested on subsequent intake.

*Metabolic Aspects of Regulation.* While day-to-day variations in individual food intake are considerable, the absorption of food and its entrance into metabolic pools influence subsequent food intake with considerable precision when considered over long-term periods of time. It is difficult to see how the gastrointestinal metering could be operative except in short-term regulation. Since many biochemical changes occur within the organism as the result of feeding, and since satiety follows consumption of a wide variety of diets of different composition, the metabolic consequences of eating are probably to be sought in long-term regulation.

The complexity of the problem is emphasized by the number of factors involved. For example, the body's stores of water and also changes in water concentration in body fluids influence the central mechanism by limiting food intake [18], perhaps by way of the "osmoreceptors" of the brain. There is recent evidence also that biochemical changes occur within the hypothalamus itself in hungry and fed animals. Forrsberg and Larsson observed that in hungry rats the concentration of adenosinetriphosphate and creatine phosphate increased eightfold in a relatively large area of the hypothalamus which included the "feeding center" [19].

It is therefore unreasonable to expect that there is but *one* metabolic determinant for food intake. Indeed, many factors have been suggested to account for the metabolic aspects of regulation: thermal stress, glucose utilization, fat depots and levels of metabolites in the blood among them.

Brobeck, who views food intake within the perspective of over-all energy exchanges, has emphasized the thermal aspects of the problem. "Both food and work represent important sources of heat for the organism, and the amount of food eaten or muscular activity undertaken is determined in part by the animal's need for heat and its ability to lose heat to the environment"

[20]. Although this point of view has been criticized by Kennedy [5] who observed that the rate of accumulation of fat stores by hypothalamic rats when acclimatized was relatively unaffected by environmental temperature, it should be noted that for Strominger and Brobeck [21] this is not a matter of direct calorimetry by the hypothalamus. It is not calories *per se* that are being measured, but the extra heat released by the assimilation of food, the well known specific dynamic action. Since the hypothalamus contains cells that respond to an increase in temperature, and since eating is followed by a slight rise in central and a greater rise in cutaneous temperature, these workers believe that the evidence supports the older hypothesis of Strang and McClugage [22], that the principal but not only factor in satiety is the stress imposed upon the body by the specific dynamic action of the absorbed food. The importance of this mechanism has not been established; it would appear to contribute to short-term regulation.

*Glucose Metabolism and Food Intake.* No recent area has been more controversial than this, and the account presented here is by a not entirely detached observer. The non-controversial fact is that marked hypoglycemia, whether occurring spontaneously or insulin-induced, is associated with hunger sensations in man, and increased food intake in men and animals. In view of the limited carbohydrate stores of the body and the fact that the central nervous system is glucose-dependent, we have proposed that hypoglycemia is an emergency mechanism in the regulation of food intake, not operating in the physiologic range of blood sugar, and analogous to anoxemia in the regulation of respiration [7].

Mayer [6] and his colleagues have presented the hypothesis that there are "glucoreceptors" in the ventromedial hypothalamus which are "sensitive to blood glucose in the measure that they can utilize it." For these workers arterio-venous glucose differences (" $\Delta$  glucose") in the periphery serve as a measure of utilization by the receptors in the hypothalamic satiety center. They have demonstrated a good correlation between satiety and elevated  $\Delta$  glucose values; the data available on insulin-induced hunger are difficult to rationalize with the hypothesis however.

Mayer has interpreted the evidence of Forrsberg and Larsson already cited as supporting the glucostatic hypothesis. Larsson [23] interprets his data as evidence of an increase in blood flow

to the feeding and adjacent centers in the hypothalamus, and related to an increase in over-all activity rather than to the activity of the postulated "glucoreceptors."

The conflicting evidence on blood glucose levels (spontaneous variations, glucose-induced hyperglycemia or insulin-induced hypoglycemia), hunger sensations and gastric hunger contraction has been critically reviewed by Grossman [4]. The crucial evidence in the last analysis must relate to food intake. Controlled evidence in man suggests that hyperglycemia resulting from intravenous glucose infusions with elevated  $\Delta$  glucose values did not significantly depress food intake in normal human subjects [24].

The recent observations by Stunkard, Van Italie and Reis that glucagon given intravenously diminished hunger sensations and gastric contractions in human subjects [25], and the findings by Schulman and his colleagues that intramuscular glucagon diminished food intake in man have raised the problem anew [26]. These effects, however, like the inhibitory effect of glucagon on gastric secretion, may occur with doses producing relatively small rises in peripheral blood sugar levels.

*Fat Depots and Food Intake.* On the basis of studies in aging animals, and animals made obese by hypothalamic lesions, Kennedy has suggested that the "hypothalamus satiety mechanism is concerned only with the prevention of an over-all surplus of energy intake which would cause the deposition of fat in the depots. The simplest way in which this lipostasis could be achieved is by sensitivity to concentration of circulating metabolites" [5]. In this account the amount of depot fat influences the hypothalamus by way of the level of blood metabolites, a mechanism made possible by the rapid turnover between stores and blood. This hypothetical mechanism could play a role in long-term regulation but is vague as to the nature of the metabolites in question.

A reciprocal relationship between amino acid concentration and appetite has also been reported [27]. Dole and his co-workers [28] have demonstrated a rather impressive straight line relationship between daily protein intake and daily caloric intake of unrestricted non-protein foods. In their account appetite is influenced by over-all metabolic stores, the "metabolic inventory."

The crux in all these accounts is how the central nervous system receives the necessary information regarding the body's content of

nutrients. This might be accomplished by neural impulses from the stores, since connections between the hypothalamus and the fat depots are believed to exist by way of sympathetic afferents [29]. The information also could be carried by the blood stream, but no single metabolite or combination of metabolites has clearly been shown to relate this knowledge.

#### AN ATTEMPT TO SUMMARIZE THE PRESENT STATUS

Only a multiple factor analysis can attempt to do justice to the complexity of the problem of regulation of food intake. It is obvious that the present account has not touched on the psychologic and cultural forces influencing food-taking behavior. With this as a preamble, one might hazard the following formulation: At the physiologic level of regulation of intake, deficits of the body's stores of calorically significant nutrients activate feeding reflexes which are facilitated by areas in the lateral hypothalamus, and inhibited by the ventromedial hypothalamus. These deficits concomitantly give rise to hunger sensations which may be cues for food intake (the epigastric pang associated with the gastric hunger contraction being a dispensable component of the complex of disagreeable sensations). These hypothalamic centers are sensitive to local temperature and appear to be influenced by body stores of water.

Day-to-day regulation of the amount of food consumed is metered in part by oropharyngeal receptors, and the size of an individual meal is controlled by gastric and upper intestinal receptors responding to distention probably mediated by the vagus.

The hypothalamic areas are also believed to be influenced by the metabolic consequences of food absorbed and assimilated. The specific dynamic action of food, the utilizable blood glucose, the concentration of other metabolites in the blood, the level of protein of the diet and depot fat have all been proposed as cues to the central nervous system, but none have been firmly established as governing short- or long-term control.

#### INTAKE OF WATER AND INTAKE OF FOOD

Since there is a very close correlation between food intake and water intake in normal and hypothalamically injured animals, it may be useful at this point to compare the rough generalizations of the immediately preceding paragraphs with current knowledge regarding the physiologic regulation of water intake [30].

The body's content of water is governed not only by overflow of excesses but also by adjustment of intake [37]. The regulation of the volume imbibed is precise and adjustments in most species are made rapidly. Water deficits give rise to the urge to drink, thirst being conceived of as the awareness of the need to drink. Two stimuli have been clearly defined. One is cellular dehydration secondary to water deficits (extracellular hyperosmolarity may be but is not necessarily associated with this situation) and the other is a contraction of the extracellular fluid volume (which may be associated even with hypotonicity of the body fluids). Thirst monitors not only the composition of fluids in the body but is concerned also with their volume. These osmotic and volumetric stimuli appear to act through areas in the hypothalamus which have been stimulated experimentally by local hypertonic fluid or electrically [32].

Water deficits are regularly accompanied by reductions in salivary flow. The resulting dry mouth is a powerful stimuli to water intake [33]. As with food, metering of the volume of fluid taken is accomplished by passage of water through the oropharynx (sham drinking gives temporary satisfaction) and gastric distention further inhibits additional water drinking. The stretch receptors already cited are probably involved since vagotomy abolishes this phenomenon [34].

In contrast to food intake, water drinking is less embroiled in linguistic controversy; the adjustments are essentially short-term; the stimuli have been defined with greater precision; the local sensation of dry mouth is a more powerful cue than the gastric hunger contraction and epigastric pang. The neural centers of drinking, however, are less clearly demarcated. In the regulation of both food and water intake oropharyngeal and gastric metering is accomplished in part by stretch receptors via the vagus. It is probably significant of their close relationship that the sympathomimetic amine, amphetamine, inhibits both food and water intake [35].

#### FUNCTIONAL DISTURBANCES OF REGULATION

The anorexia of disease ought to be explicable in terms of functional disturbances of the central regulatory mechanism caused by fever, toxins, abnormal metabolites, etc., but little has been established. The striking loss of appetite in hepatitis remains unexplained.

The pharmacology of anorexia-producing drugs of the amphetamine group is slightly

better understood. Although amphetamine administration will reduce food intake in mice with goldthioglucose obesity [36], and in rats with surgical lesions of the hypothalamus [37]. Brobeck, Larsson and Reyes have detected an increase in electrical activity of the ventromedial nucleus (the "satiety center") following administration of the drug [38]. This may be an indirect effect mediated by impulses arising in the prefrontal areas of the cerebral cortex, since incomplete "prefrontal lobotomy" in the dog raised the threshold for this drug [35]. This evidence is in keeping with the finding of Harris, Ivy and Searle that patients with the bulimia of prefrontal lobotomy are less responsive to amphetamine [39].

Probably the most important impetus to modern study of the regulatory mechanism for food intake has been the belief that this is a fruitful approach to the problem of obesity. Indeed Mayer and his colleagues have introduced the general distinction between "regulatory" obesities and "metabolic" obesities, the primary disturbance in the former being in the central mechanism regulating food intake [40]. The animal examples of this regulatory disturbance exist in the hereditary obesity of the yellow mice of the Danforth strain, and animals with chemical (goldthioglucose) or surgically-induced lesions of the hypothalamus. It is reasonable to suppose, as Tepperman recently has suggested, that some individuals inherit central regulating mechanisms "that work better than do those of other people. It is not difficult to imagine that variability in function of this piece of regulating equipment may be such as to permit a small cumulative error in metering" [36]. Yet, aside from individuals with lesions of the frontal lobes, frontal lobotomy, or with tumors of the base of the brain, there is no convincing evidence of disturbance of the central regulatory machinery in most human obesity, although it is widely assumed that "psychogenic" obesity is of the regulatory type.

It has not been the purpose of this schematic outline to decry this concern, with obesity, but rather to emphasize that food-taking is a homeostatic mechanism capable and worthy in itself of being studied along with the many other physiologic regulations of the body.

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# Clinical Studies

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## Subacute Hepatic Necrosis and Postnecrotic Cirrhosis Due to Anicteric Infections with the Hepatitis Virus\*

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CHARACTERISTICALLY the lesions of acute viral hepatitis heal without scarring, a fortunate circumstance apparently related to the self-limited character of the infection, the relatively small size of the individual foci of necrosis, and preservation of the supporting reticulum, features which permit rapid regeneration and restoration of the normal lobular architecture. However, when the zones of necrosis are large, and involve whole lobules or groups of contiguous lobules, as is known to occur in the more florid and usually protracted form of viral hepatitis that produces subacute hepatic necrosis (subacute yellow atrophy), there is collapse and ultimate "collagenization" of the supporting stroma, and nodular hyperplasia of the surviving parenchyma. This gives rise to a form of cirrhosis in which the liver is studded with coarse nodules separated by broad bands of connective tissue. Occasionally, when the zones of necrosis bridge small groups of lobules in a symmetrical pattern, fine scarring and nodulation result, giving the liver a granular appearance. During the early stage of subacute hepatic necrosis the liver shows the characteristic histological features of acute viral hepatitis but once extensive scarring and nodulation have occurred the postnecrotic cirrhosis produced cannot be distinguished from that due to other causes, such as hepatotoxins, drug reactions, and metabolic disorders like the deToni-Fanconi syndrome and Wilson's disease. It is obvious, therefore, that a viral etiology cannot be established on morphological grounds alone unless the lesion is seen early in the course of the infection.

On the basis of autopsy experience it has been

estimated that approximately 10 per cent of all cases of cirrhosis seen in this country are of the postnecrotic variety [1]. In only a small fraction of these can the etiology be established with certainty. However, there is an impression, based largely on circumstantial clinical and epidemiological evidence, that the hepatitis virus may be responsible for a high proportion of such cases. Certainly when the cirrhosis follows closely on the heels of a typical attack of acute viral hepatitis with jaundice, there can be little doubt about the etiology. However, in most cases there is no history of antecedent jaundice, so that if the virus is to be implicated it must be assumed that it is capable of producing subacute hepatic necrosis without jaundice. It is well known that anicteric infections do occur, and that the lesions produced are identical with those seen in the usual form of the disease [2] but there are relatively few instances in which classic subacute hepatic necrosis and progression to postnecrotic cirrhosis have been demonstrated [3-5]. One problem has been the difficulty in recognizing such infections sufficiently early, so that most cases of postnecrotic cirrhosis of presumed viral origin are first seen when the lesions no longer show the characteristic features of viral hepatitis.

The purpose of this report is to draw attention to the clinical and morphological features of anicteric infections with the hepatitis virus that give rise to subacute hepatic necrosis and postnecrotic cirrhosis. It is based on a study of nine patients with a prolonged anicteric illness of relatively abrupt onset in whom histological study revealed subacute hepatic necrosis with

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features indicative of a viral origin, and progression to cirrhosis. Experience with this group suggests that such infections are easily overlooked or misinterpreted, and hence may be responsible for instances of otherwise unexplained cirrhosis.

TABLE I  
TYPES OF CIRRHOSIS ENCOUNTERED IN 413 PATIENTS  
INVESTIGATED BOTH CLINICALLY AND HISTOLOGICALLY

I. Laennec's . . . . .	267 (64.6%)*
II. Postnecrotic† . . . . .	69 (16.7%)
A. Presumably viral	
1. Acute onset with jaundice—40	
2. Acute anicteric onset—12	
3. Insidious onset—11	
B. Toxic—3	
C. Drug sensitization—3	
III. Biliary . . . . .	24 (5.8%)
A. Primary—8	
B. Secondary—16	
IV. Hemochromatosis . . . . .	18 (4.4%)
V. Cardiac . . . . .	6 (1.5%)
VI. Granulomatous . . . . .	6 (1.5%)
A. Sarcoidosis—4	
B. Brucellosis—2	
VII. Wilson's disease . . . . .	2 (0.5%)
VIII. Unclassified . . . . .	21 (5.0%)

\* Figures in parentheses represent % of total group.

† Including subacute hepatic necrosis.

#### MATERIAL AND METHODS

The nine cases to be described were encountered in a group of sixty-nine patients with subacute hepatic necrosis and/or postnecrotic cirrhosis studied both clinically and histologically between 1948 and 1957, a period during which a total of 413 cases of cirrhosis were similarly investigated. (Table I.) These cases were selected for presentation because they had the following features in common: (1) relatively abrupt onset that could be dated with reasonable accuracy, (2) absence of clinically detectable jaundice for at least the first three months of illness, (3) a history of an adequate dietary intake and of complete abstinence or only negligible consumption of alcohol, (4) no known exposure to hepatotoxins or drugs, (5) no signs of hepatolenticular degeneration or family history of either hepatic or neurological disease, and (6) changes in the liver consistent with the diagnosis of subacute hepatic necrosis and/or postnecrotic cirrhosis of viral origin. In each case biopsy material was obtained sufficiently early in the course of the disease to demonstrate the characteristic features of viral hepatitis. The histological criteria used were essentially those described by Mallory [2], Dible, McMichael and Sherlock [6], and Axenfeld and Brass [7] for acute viral hepatitis, and by Lucké [8], Mallory [9], and

Baggenstoss and Stauffer [10] for subacute hepatic necrosis and postnecrotic cirrhosis of viral origin.

Specimens of liver, obtained by the Vim-Silverman needle biopsy technic or by direct surgical excision, were fixed in either Carnoy's solution or neutral formalin, and stained routinely with (1) hematoxylin and eosin, (2) Masson's trichrome stain, (3) Laidlaw's silver stain for reticulum, (4) van Gieson's stain for collagen, and (5) Gomori's stain for hemosiderin.

Three representative cases are presented in detail. The clinical and morphological features in the group as a whole are summarized in the sections that follow.

#### CASE REPORTS

CASE I. W. R., a fifty-two year old housewife, was admitted to the hospital on June 5, 1951, with the complaint of rapid enlargement of the abdomen of one week's duration. In March, 1951, three months prior to this admission, the patient had experienced a three-day attack of severe crampy epigastric pain unaccompanied by fever, anorexia, vomiting or diarrhea. For a few days following subsidence of the pain the urine had been slightly darker and the stools slightly lighter than normal. However, a physician who examined the patient at that time could find no evidence of jaundice or hepatomegaly. During the succeeding three months the patient had felt perfectly well, and had been able to carry out her usual household duties without undue fatigue. However, she had occasionally noted a mild sensation of pressure high in the epigastrium.

Abnormal distention due to ascites had appeared rather suddenly one week before admission, and had increased at a rapid rate. This was accompanied by slight ankle edema, dyspnea and orthopnea, but there were no associated constitutional or gastrointestinal symptoms.

Rheumatoid arthritis involving many joints had been present since the age of fifteen years, but had not been disabling for many years. Menses, which had been regular until March, 1951, ceased with the onset of the present illness.

On physical examination the patient was thin and pale, but showed no signs of wasting and did not appear ill. No icterus was evident, and the skin was free of spider nevi, plamar erythema or abnormal pigmentation. There were signs of a small pleural effusion bilaterally. The heart appeared normal. The abdomen was greatly distended, the presence of fluid making palpation difficult. Following paracentesis, hepatosplenomegaly was noted. The edge of the liver, which was thin, firm, smooth and non-tender, could be felt one fingerbreadth below the right costal margin in the mid-clavicular line and 3 fingerbreadths below the xiphoid in the midline. A firm rounded splenic tip was palpable 2 fingerbreadths below the costal margin deep in the left flank. No venous collaterals were visible over the abdominal wall. The lymph nodes

were not enlarged. The interphalangeal joints were thickened and stiff, and motion in the wrist, elbow, shoulder and hip joints was limited. Moderate pitting edema was present about the ankles. There was no clubbing.

The urine was of normal color and contained no bile, sugar, albumin or formed elements. Stools were of normal color and gave a negative guaiac test. There were 3,660,000 red blood cells per cu. mm., 4,150 white blood cells per cu. mm. and the differential count was normal. The results of liver function tests were grossly abnormal (Table II), and were considered indicative of hepatocellular disease. X-ray films of the chest showed a small pleural effusion bilaterally. Gastrointestinal x-ray films were normal, with no evidence of esophageal varices. The gall-bladder was non-filling.

Several diagnostic possibilities were considered, including intra-abdominal malignancy, portal vein thrombosis and amyloidosis. However, needle biopsy of the liver, carried out on June 21, 1951, revealed the typical features of early active subacute hepatic necrosis consistent with a recent infection with hepatitis virus. The parenchyma was subdivided into large islands of varying shapes by broad septums containing numerous small thin-walled blood vessels, proliferating bile ducts, lymphocytes, and plasma cells. (Fig. 1.) Sections stained for reticulum and collagen revealed that the septums represented zones of recent collapse in which compressed reticulum fibers and sinusoids predominated. (Fig. 2.) A few bundles of thick collagen fibers encircled the portal triads in the areas of collapse. The surviving parenchymal cells were normal in some areas but in others were arranged in an irregular pattern of thick plates, and showed unusual variations in size, patchy acidophilic staining and karyolysis. Scattered through the parenchymal masses were a number of typical acidophilic bodies. [2,7] and small foci of mononuclear leukocytes and proliferating Kupffer cells. (Figs. 3 and 4.)

Following paracentesis the patient was relieved of her dyspnea and appeared well except for a low grade intermittent fever with temperatures up to 101°F. On a high-protein, vitamin-supplemented diet and a sodium intake of approximately 200 mg. daily, some of the edema disappeared but the ascites did not clear completely.

Once the nature of the hepatic lesion was established a two-week course of intravenous ACTH was begun. The temperature promptly dropped to normal but returned to its previous level soon after the cessation of therapy. A second needle biopsy of the liver, carried out on July 10, 1951 following ACTH therapy, showed the same distortion of the lobular architecture which had been noted a month earlier. However, there was a marked decrease in the inflammatory exudate, and the trabeculae appeared more compact and less vascular, and now contained numerous thick collagen

TABLE II  
LIVER FUNCTION TESTS IN CASE I

Date of Test	Serum Bilirubin		Brom- sulphalein Retention (%)	Cephalin- Cholesterol Flocculation	Thymol Turbidity (units)	Serum Alka- line Phos- phate (SJR units)	Serum Proteins			Serum Cholesterol			Prothrom- bin (%)	Urine	
	1-minute (mg. %)	Total (mg. %)					Total (gm. %)	Albumin (gm. %)	Globulin (gm. %)	Total (mg. %)	Free (mg. %)	Free (%)		Bile	Urobilinogen (Ehrlich units)
6/6/51	0.60	1.76	61	3+	35	10.2	6.5	2.2	4.3	181	64	35	50	0	0.92
6/15/51	0.68	1.96	44	3+	31	10.3	6.5	2.5	4.1	50	0	35	50	0	1.19
6/25/51	0.40	1.30	44	2+	23	9.7	5.9	2.2	3.8	50	0	64	50	0	1.47
7/2/51	0.45	1.76	42	2+	27	9.8	5.9	2.2	3.8	50	0	64	50	0	3.20
7/9/51	0.58	1.88	42	3+	19	8.6	7.2	2.7	4.5	35	4+	34	50	0	2.45
7/13/51	0.54	1.78	..	2+	19	7.2	7.2	2.7	4.5	35	4+	34	50	0	0.50
8/28/51	5.41	10.1	..	4+	23	17.8	7.2	2.7	4.5	35	4+	34	50	4+	2.70
9/11/51	8.55	16.4	..	4+	27	10.6	7.2	2.7	4.5	35	4+	34	35	4+	2.13
9/25/51	7.16	15.5	..	4+	38	17.3	7.2	2.7	4.5	35	4+	34	35	4+	2.13
10/9/51	4.04	9.54	..	4+	37	12.9	7.2	2.7	4.5	35	4+	34	35	4+	2.13
11/27/51	2.32	4.96	..	4+	33	15.8	7.2	2.7	4.5	35	4+	34	35	4+	2.13
2/5/52	1.24	2.96	..	4+	26	11.2	7.2	2.7	4.5	35	4+	34	35	4+	2.13
5/20/52	0.37	1.08	..	4+	22	12.2	6.6	2.5	4.1	235	80	34	35	4+	2.13
8/6/52	0.43	1.48	44	4+	18	10.8	6.5	2.8	3.7	235	80	34	35	4+	2.13
9/17/52	0.45	1.52	..	4+	20	9.0	6.5	2.8	3.7	235	80	34	35	4+	2.13
10/29/52	0.30	1.08	..	4+	18	9.4	6.9	3.5	3.3	235	80	34	35	4+	2.13
6/26/53	0.24	1.18	..	4+	14	9.1	6.9	3.5	3.3	235	80	34	35	4+	2.13
6/2/54	0.59	1.52	40	4+	10	7.9	6.0	1.9	4.1	235	80	34	35	4+	2.13
3/22/55	3.83	11.2	..	2+	4	3.0	4.7	2.2	2.5	235	80	34	35	4+	2.13
3/24/55	11.7	23.8	..	3+	9	8.2	4.7	2.2	2.5	235	80	34	35	4+	2.13
3/25/55	11.5	21.8	54	4+	9	8.8	4.7	2.2	2.5	235	80	34	35	4+	2.13
3/28/55	10.6	19.7	62	4+	8	6.2	4.7	2.2	2.5	235	80	34	35	4+	2.13

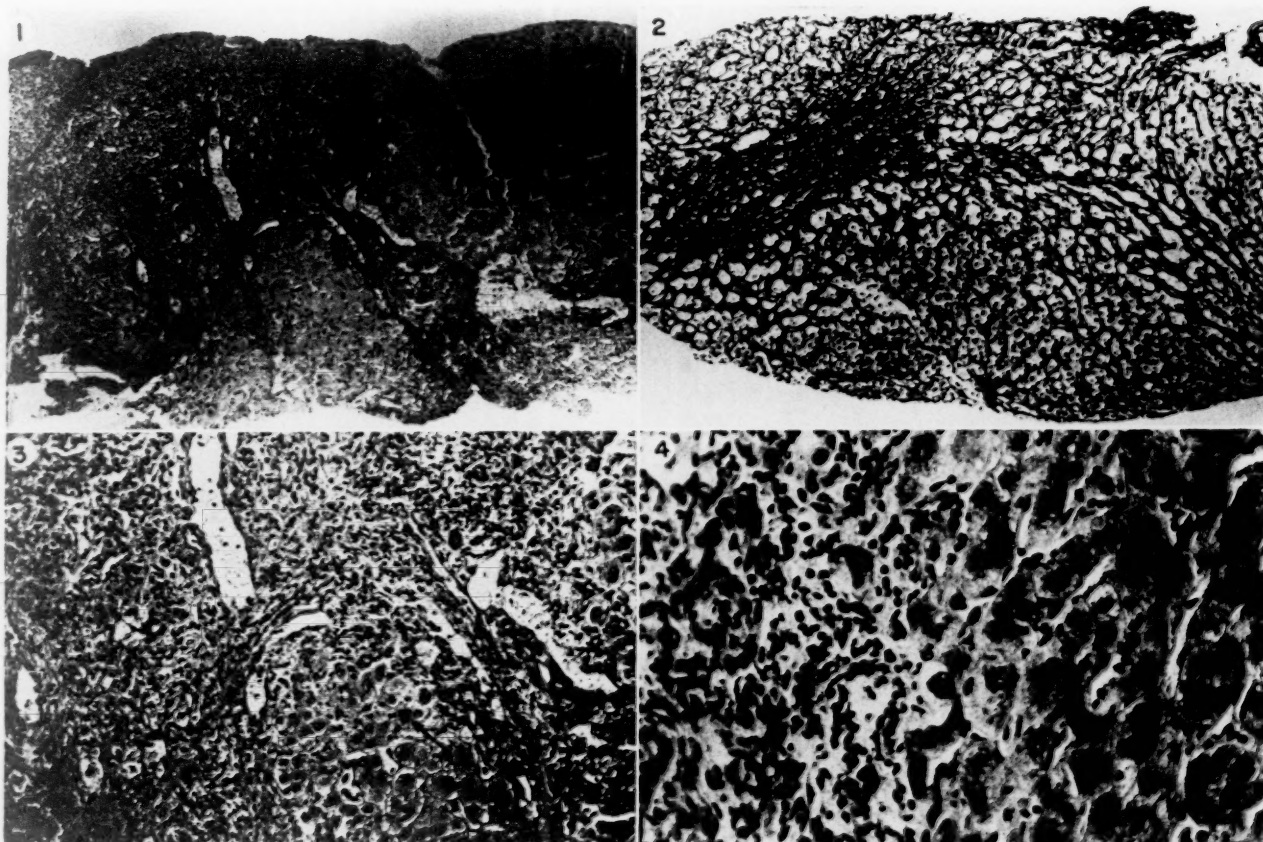


FIG. 1. Case I. Needle biopsy specimen of liver obtained three months from the onset of illness. Parenchymal nodules separated by broad zones of necrosis and collapsed reticulum heavily infiltrated with mononuclear cells. Masson stain, original magnification  $\times 100$ .

FIG. 2. Case I. Silver stain of section illustrated in Figure 1 to show collapsed reticulum in a zone of necrosis. Laidlaw stain, original magnification  $\times 100$ .

FIG. 3. Case I. Higher magnification of section illustrated in Figure 1 showing a small island of parenchymal cells containing an early acidophilic body (arrow) surrounded by a broad zone of necrosis in which collapsed sinusoids are still evident. Note the pleomorphism of the parenchymal cells, the presence of binucleate cells and the intense mononuclear reaction involving both the parenchyma and the stroma. Masson stain, original magnification  $\times 200$ .

FIG. 4. Case I. Detail of the edge of a nodule illustrated in Figure 1. The adjacent stroma contains numerous small proliferating bile ducts surrounded by lymphocytes, histiocytes and plasma cells. The parenchymal cells show marked variations in size and staining quality, irregularities in their arrangement and the presence of double nuclei. Swelling and multiplication of the Kupffer cells are evident in some of the sinusoids. Hematoxylin and eosin stain, original magnification  $\times 400$ .

bundles. Serial liver function studies made during this period showed a slight decrease in bromsulphalein retention, thymol turbidity reaction, and serum globulin, but the serum albumin and prothrombin levels remained low. (Table II.)

The patient was discharged from the hospital on July 17, 1951, and was referred to the Outpatient Department where she was seen at frequent intervals during the following three and a half years. Despite limited activity the patient noted unusual fatigue as soon as she returned to her home. One month later, or five months following the onset of illness, jaundice, anorexia and weight loss were noted for the first time. The jaundice deepened, reaching a peak in three weeks, and was accompanied by dark urine, light

stools and pruritus. Concomitantly, there was an increase in the previously noted ascites despite rigid restriction of sodium. Icterus slowly subsided during the succeeding four months but the serum bilirubin did not return to a normal level until four months later. (Table II.)

Throughout the remaining course of the patient's illness ascites was the major problem. Dietary measures and diuretics were only partially effective, so that many paracenteses were required for relief of abdominal discomfort. Peripheral edema was never prominent. Anorexia and fatigability fluctuated in severity, but were always present. It was difficult to assess the patient's true weight because of fluid retention, but progressive tissue wasting soon became ob-

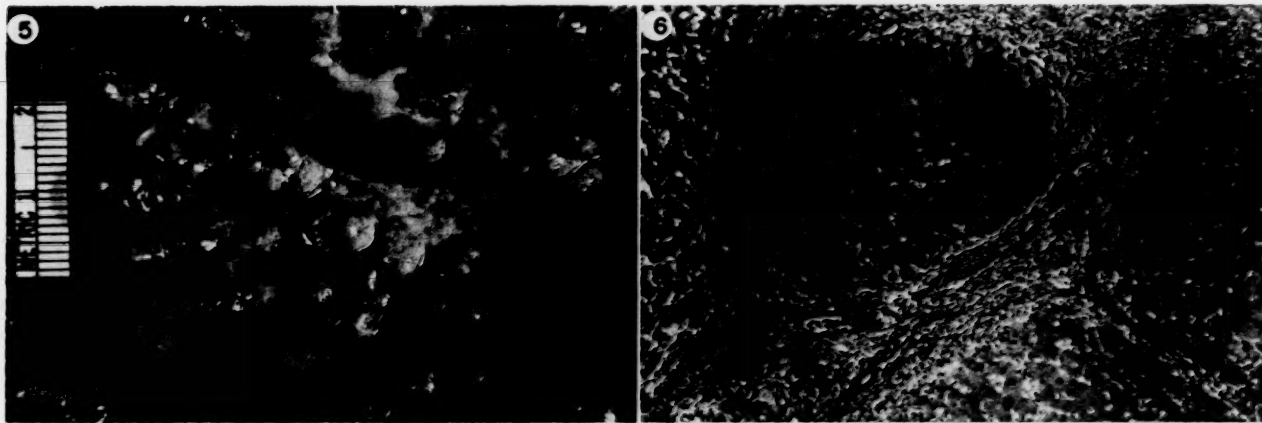


FIG. 5. Case 1. Gross appearance of the liver at autopsy four years after the onset of illness. Note the large multilobulated nodules and broad depressed scars.

FIG. 6. Case 1. Microscopic section of specimen illustrated in Figure 5 demonstrating large parenchymal nodules surrounded by broad bands of connective tissue containing numerous mononuclear cells and a small number of bile ducts. Masson stain, original magnification  $\times 100$ .

vious. At no time were spider nevi or palmar erythema noted. The presence of esophageal varices was demonstrated radiographically for the first time in March, 1954. One year later, on March 21, 1955, the patient had a massive hematemesis and was promptly readmitted to the hospital. The only new findings of note were recurrence of jaundice, the presence of distended abdominal venous collaterals, and a nodule on the anterior surface of the liver. Despite tamponade of the esophagus, multiple transfusions, massive ACTH therapy, and the administration of antibiotics and intravenous sodium glutamate, the jaundice deepened and the patient lapsed into coma. Death ensued on March 29, 1955, just four years after the onset of illness.

At autopsy the liver was coarsely nodular and weighed 1,000 gm. (Fig. 5.) The individual nodules varied in size from 0.5 to 4.0 cm. in diameter, and were separated by dense bands of connective tissue. On microscopic examination the nodules were composed of large masses of relatively normal appearing parenchymal cells with scattered acidophilic bodies and numerous centrally located foci of degeneration and necrosis. (Fig. 6.) In some of the nodules eccentrically-placed normal-appearing portal triads and central veins could be identified. The connective tissue septums, which were composed of bundles of thick collagen fibers, contained numerous lymphocytes, plasma cells and proliferating bile ducts. (Fig. 7.) Considerable subcapsular fibrosis was present. The gallbladder was thickened and contained one stone. The spleen was enlarged, weighing 500 gm. It had a thickened capsule and exhibited congestion and reticuloendothelial hyperplasia. Esophageal varices were demonstrated but no bleeding site could be found. However, there was an acute ulceration of the lesser curvature of the stomach close to the cardia, probably due to pressure necrosis resulting from the prolonged use of an esophageal balloon.

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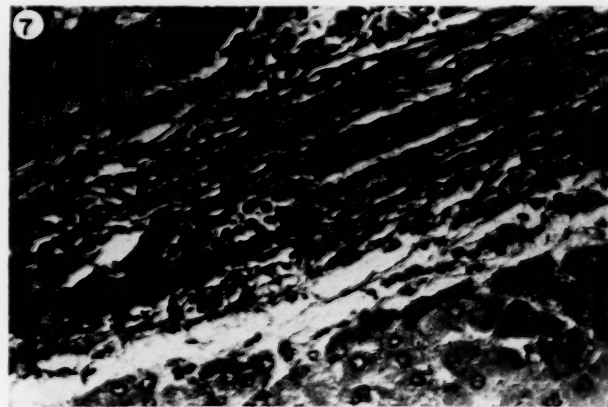


FIG. 7. Case 1. Higher magnification of section illustrated in Figure 6 to show the presence of dense collagen fibers in the stroma surrounding the parenchymal nodules. Masson stain, original magnification  $\times 400$ .

*Comment:* The onset of hepatitis in this case was acute, and was characterized by a brief episode of abdominal pain and a change in the color of the urine and stools. The diagnostic significance of these manifestations was not appreciated at the time since there was no jaundice or any of the other usual features of acute hepatitis. Indeed, it was only three months later that the sudden appearance of ascites first suggested the presence of liver disease. Of particular interest is the fact that the patient felt perfectly well for a period of four months in the face of extensive hepatic necrosis, and that jaundice did not appear until the fifth month, and then only transiently, despite obvious progression of the hepatic lesion. Death, which occurred four years after onset, was due

to progressive hepatocellular failure and terminal bleeding from esophageal varices. ACTH therapy was without significant effect, but in retrospect the dose and the duration of treatment appear to have been inadequate.

CASE III. M. B., a forty-two year old housewife, entered the hospital on November 1, 1954, because of abdominal swelling of six weeks' duration. In 1950, four years prior to this admission, the patient had had recurrent attacks of postprandial nausea and vomiting. There had been no accompanying pain, fever, jaundice or pruritus. However, a cholecystogram had revealed the presence of numerous stones. Accordingly, cholecystectomy had been carried out in January, 1951, with prompt relief of symptoms. At operation the appearance of the liver was said to have been normal. Except for occasional eructations following the ingestion of fried and fatty foods, the patient had been perfectly well for a period of three years.

In April, 1954, there had been a return of nausea and retching, particularly in the early morning and after meals. Dark urine, light stools and pruritus had been noted intermittently, and the complexion had been described as sallow. However, the referring physician had been unable to detect any overt jaundice, and the icterus index and serum alkaline phosphatase levels on several occasions between April and July had been within normal limits. Anorexia had been minimal, but over the ensuing six months there had been a 30 pound weight loss. During July studies of liver function had revealed an increase in thymol turbidity to 7.2 units and a positive cephalin-cholesterol flocculation reaction.

In August, 1954, four months after the onset of symptoms, the patient had an attack of abdominal pain in the upper right quadrant which radiated to the right scapula. The pain, which was dull and constant in character and unaccompanied by chills or fever, subsided spontaneously within twenty-four hours. However, since the possibility of common duct stone could not be excluded, the patient had been admitted to another hospital for investigation. Here the principal findings had been faint icterus, slight tenderness beneath the right costal margin, and a number of abnormalities in liver function, including an increase in the icterus index to 12.4, 4-plus bilirubinuria, a 4-plus cephalin-cholesterol flocculation reaction, a thymol turbidity level of 13.5 units, and an increase in the serum alkaline phosphatase to 7.7 Bodansky units. Although the possibility of hepatocellular disease was considered, mechanical obstruction of the biliary tract appeared more likely to the attending physician, so that surgical exploration was advised. At operation, which was carried out on August 24, 1954, the common duct had appeared normal, but had contained cloudy bile. However, following insertion of a T tube there had been a free flow of clear bile. The liver, which was not enlarged, had been described as having

a finely wrinkled surface. A biopsy specimen obtained from the right lobe of the liver had been interpreted as showing acute pericholangitis, presumably due to an ascending bacterial infection of the bile ducts. Following operation and the institution of external biliary drainage, the jaundice cleared, gastrointestinal symptoms abated, and there was a significant gain in weight. In September, 1954, one month postoperatively, cholangiography revealed a normal common duct, so that the T tube was removed. At this time the patient felt well, but noted swelling of the abdomen. At first this was attributed to gaseous distention but during the next month it became evident that it was due to ascites. As the ascites increased, anorexia and nausea returned, and slight peripheral edema appeared. Diuretics and salt restriction were only partially effective, and since the diagnosis was still in doubt the patient had been referred to this hospital for further study.

On physical examination, the patient was well nourished but showed signs of recent weight loss, and looked chronically ill. There was no icterus of the skin or scleras, and spider nevi, palmar erythema and xanthomas were absent. The heart, lungs and breasts were within normal limits. A number of dilated veins were visible over the flanks. The abdomen was greatly distended with fluid, and non-tender. Neither the liver nor the spleen could be felt even after the removal of 7.2 L. of ascitic fluid.

The hemoglobin was 15.3 gm. per cent; hematocrit, 44 per cent; white blood cell count, 5,350 per cu. mm.; differential leukocyte count, normal. Urine analysis was normal except for a trace of albumin. The stool was brown in color, and gave a negative guaiac reaction. Liver function studies showed serum bilirubin, one-minute, 0.36 mg. per cent; total, 1.02 mg. per cent; bromsulphalein retention at forty-five minutes, 50.6 per cent; cephalin-cholesterol flocculation test, negative at twenty-four and forty-eight hours; thymol turbidity, 6.3 units; thymol flocculation test, 2 plus; serum alkaline phosphatase, 7.5 S-J-R\* units; urine urobilinogen, 0.13 Ehrlich units; urine bile, negative. The serum proteins totaled 6.4 gm. per cent; albumin, 2.5 gm. per cent; globulin, 3.9 gm. per cent. The total cholesterol was 202 mg. per cent; free cholesterol, 67 mg. per cent (37 per cent of the total); fatty acids, 13.6 mEq./L.; lipid phosphorus, 7.0 mg. per cent. X-ray film of the esophagus revealed the presence of small varices.

Review of the surgical biopsy specimen of the liver, obtained on August 24, 1954, in the fourth month of illness, revealed the typical features of early active subacute hepatic necrosis. Narrow trabeculae, consisting of collapsed reticulum at sites where parenchymal cells had dropped out, bridged both portal and central areas. (Figs. 8 and 9.) These were heavily

\* Shinowara, Jones and Rhinehart modification of the Bodansky method [45]; normal range of values: 2.2 to 8.6 units.

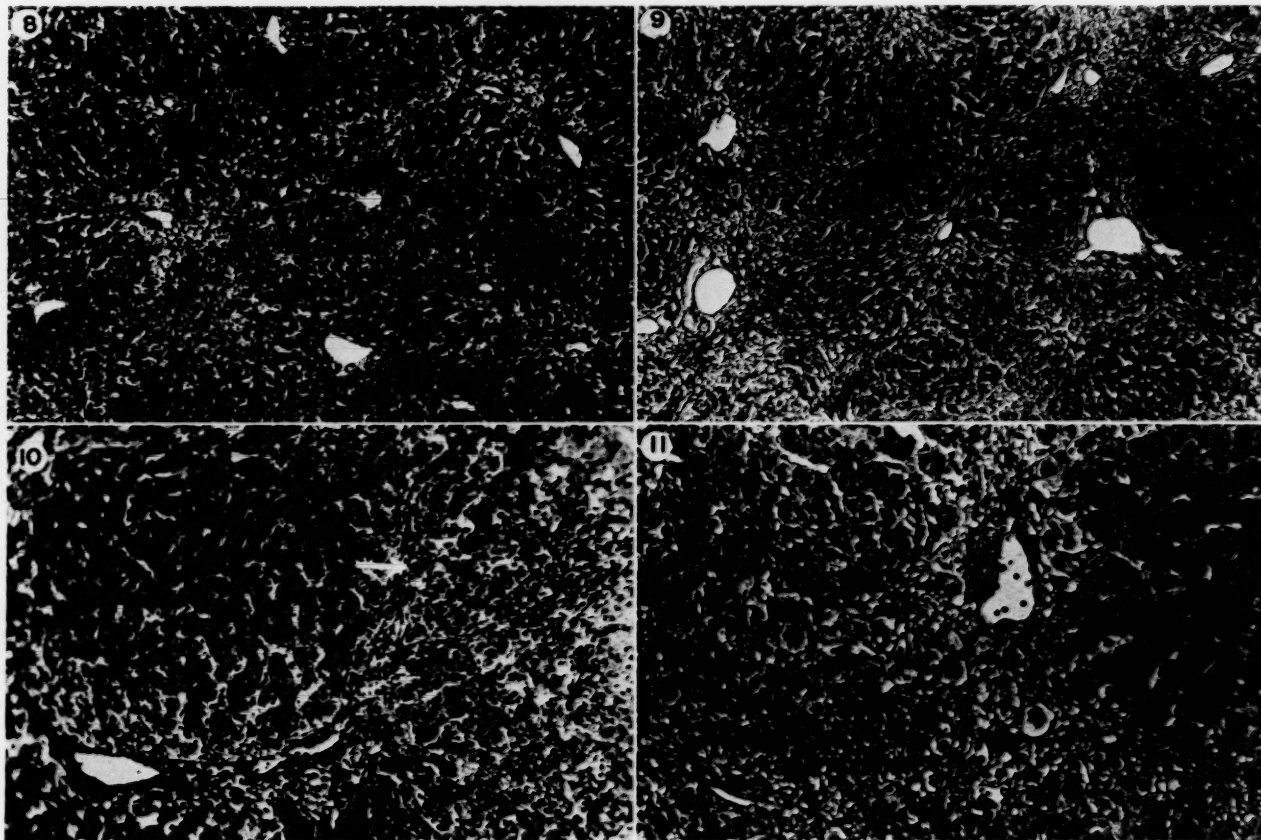


FIG. 8. Case III. Surgical biopsy specimen of the liver obtained four months after the onset of illness. Low magnification showing normal arrangement of central veins and portal triads with zones of necrosis, seen as pale areas, surrounding the central veins and bridging central and portal areas. Masson stain, original magnification  $\times 60$ .

FIG. 9. Case III. Silver stain of section illustrated in Figure 8 to demonstrate collapse of reticulum in linear zones of necrosis bridging central and portal areas. Laidlow stain, original magnification  $\times 60$ .

FIG. 10. Case III. Higher magnification of section illustrated in Figure 8 to show a linear zone of necrosis bridging a central vein (lower left) and two portal triads (upper right). Note loss of parenchymal cells, the presence of acidophilic bodies (arrow) and the cellular exudate lying in collapsed but still visible sinusoids. Masson stain, original magnification  $\times 200$ .

FIG. 11. Case III. Another high-power view of the section illustrated in Figure 8 to show an area of pericentral hepatocellular necrosis, degeneration and inflammation. Note the loss of parenchymal cells around the central vein, the marked variations in size, staining quality and arrangement of the immediately surrounding cells, the dissociation of the parenchymal cells in some areas, and the presence of numerous typical balloon cells characterized by marked swelling and cytoplasmic pallor. The inflammatory exudate, which is predominantly mononuclear, occupies the areas devoid of parenchymal cells and to a lesser extent the sinusoids in intact areas. Masson stain, original magnification  $\times 200$ .

infiltrated with mononuclear cells and contained numerous capillaries and proliferating bile ducts, but little or no collagen. The surviving parenchyma showed marked pleomorphism of the hepatic cells, with acidophilic bodies and ballooning, mononuclear infiltration and reticuloendothelial hyperplasia. (Figs. 10 and 11.) A needle biopsy specimen of the liver obtained on November 3, 1954, in the seventh month of illness, revealed similar changes. However, the trabeculae now contained a considerable number of thick collagen fibers, while the degenerative changes in the parenchyma and the diffuse inflammatory reaction were much less striking. (Fig. 12.)

During hospitalization the only other feature of note was a remittent fever with temperatures which ranged between  $99^{\circ}$  and  $101.5^{\circ}\text{F}$ . One paracentesis was performed for the relief of distention, following which the patient was returned to the care of her physician. At home, anorexia increased and the patient's general condition deteriorated. Despite marked limitation of sodium intake and the use of diuretics, ascites reaccumulated at a rapid rate necessitating three further abdominal paracenteses during the next two months. In January, 1955, jaundice recurred and deepened rapidly. This was accompanied by episodic confusion, and ultimately terminated in

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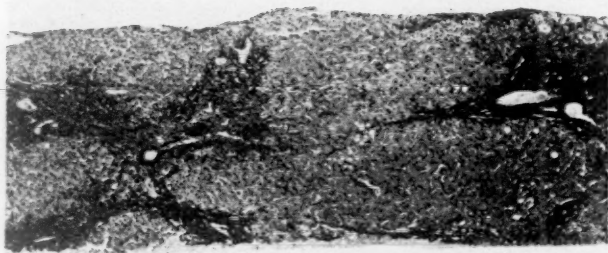


FIG. 12. Case III. Needle biopsy specimen of the liver obtained seven months after the onset of illness showing large nodules of parenchyma separated by relatively broad bands of connective tissue. The parenchymal cells are relatively normal in appearance but contain a few scattered fat droplets. The septums are heavily infiltrated with mononuclear cells, are highly vascularized and contain abundant thick collagen fibers (demonstrated with van Gieson's stain). Note the paucity of inflammatory cells in the parenchyma. Masson stain, original magnification  $\times 60$ .

deep coma. Death occurred at home in February, 1955, ten months after the onset of illness. No autopsy was performed.

*Comment:* The antecedent history of cholelithiasis, the preicteric phase of four months' duration, and the occurrence of pain in the upper right quadrant with the onset of jaundice led to the erroneous diagnosis of common duct obstruction and to ultimate surgical exploration. Despite the preoperative abnormalities of liver function suggestive of hepatocellular disease, the wrinkled appearance of the liver at laparotomy and the occurrence of ascites postoperatively, the possibility of subacute hepatic necrosis was not considered until the incorrectly interpreted surgical biopsy specimen of the liver was re-examined at a later date. The intermittency of the jaundice, as in Case I, and its relatively mild character early in the disease are noteworthy.

**CASE IV.** A. P., a forty-eight year old housewife, was referred to the hospital on September 4, 1957, for investigation of jaundice of approximately one year's duration. The patient had been perfectly well until February, 1954, when epigastric distress had developed which was relieved by food and alkali. There had been no fever, jaundice, or change in the color of the urine or stools. Two months later, because of persistence of these symptoms, the patient had been admitted to another hospital for investigation. No hepatomegaly or jaundice had been noted, and cholecystography had revealed a normally function-

ing gallbladder. However, a duodenal ulcer had been demonstrated radiographically. An ulcer regimen had promptly relieved the symptoms but there had been a recurrence within three months, so that the patient had been hospitalized for a second time. There were no new physical findings, and once again a deformed duodenal cap and normal cholecystogram were demonstrated. Strict adherence to a bland diet and antispasmodics resulted in subsidence of the symptoms for a period of almost one year.

In September, 1955, two years before the present admission, there was sudden onset of fatigability and almost constant epigastric pain relieved by food. There was no accompanying fever, weight loss, jaundice or change in the color of the urine or stools. Physical examination revealed no jaundice or hepatomegaly. However, tests of liver function demonstrated a number of abnormalities, including a serum bilirubin concentration of 1.4 mg. per cent, 1-plus bile in the urine, a serum alkaline phosphatase level of 9.4 Bodansky units, and a 3-plus cephalin-cholesterol flocculation reaction. X-ray studies at this time failed to demonstrate the previously described ulcer but once again the gallbladder filled and emptied normally. A short period of bedrest was followed by apparent recovery. However, eight months later, in May, 1956, fatigability recurred and was accompanied by persistent anorexia, weight loss and dyspnea on exertion. In October, 1956, the patient had a three-day episode of fever and chills, and for the first time overt jaundice developed. When hospitalized shortly thereafter she was found to have hepatomegaly, jaundice, a serum bilirubin concentration of 7.5 mg. per cent, a serum alkaline phosphatase level of 8.0 Bodansky units, and a 4 plus cephalin-cholesterol flocculation reaction. Cholecystography showed poor concentration of dye in the gallbladder and the presence of what was interpreted as a large non-opaque stone. Accordingly, on November 28, 1956, exploratory laparotomy was carried out; the preoperative diagnosis was obstructive jaundice due either to common duct stone or to carcinoma of the pancreas. At operation the liver was found to be enlarged and studded with soft yellow-brown nodules measuring up to 1 cm. in diameter. The common duct and gallbladder appeared normal. A liver biopsy specimen, which was subsequently reviewed, showed the classic features of subacute hepatic necrosis with large areas of collapse, an intense inflammatory reaction, prominent hepatocellular degenerative changes, numerous acidophilic bodies and signs of regeneration. (Figs. 13, 14, 15 and 16.) Most of the trabeculae lying between the parenchymal nodules were composed of a loose meshwork of collapsed reticulum containing numerous mononuclear inflammatory cells and regenerating bile ducts. However, a few of the septums contained dense collagen bundles, suggesting that the process was older than the overt jaundice, which had been present for only a few weeks, and that it probably had

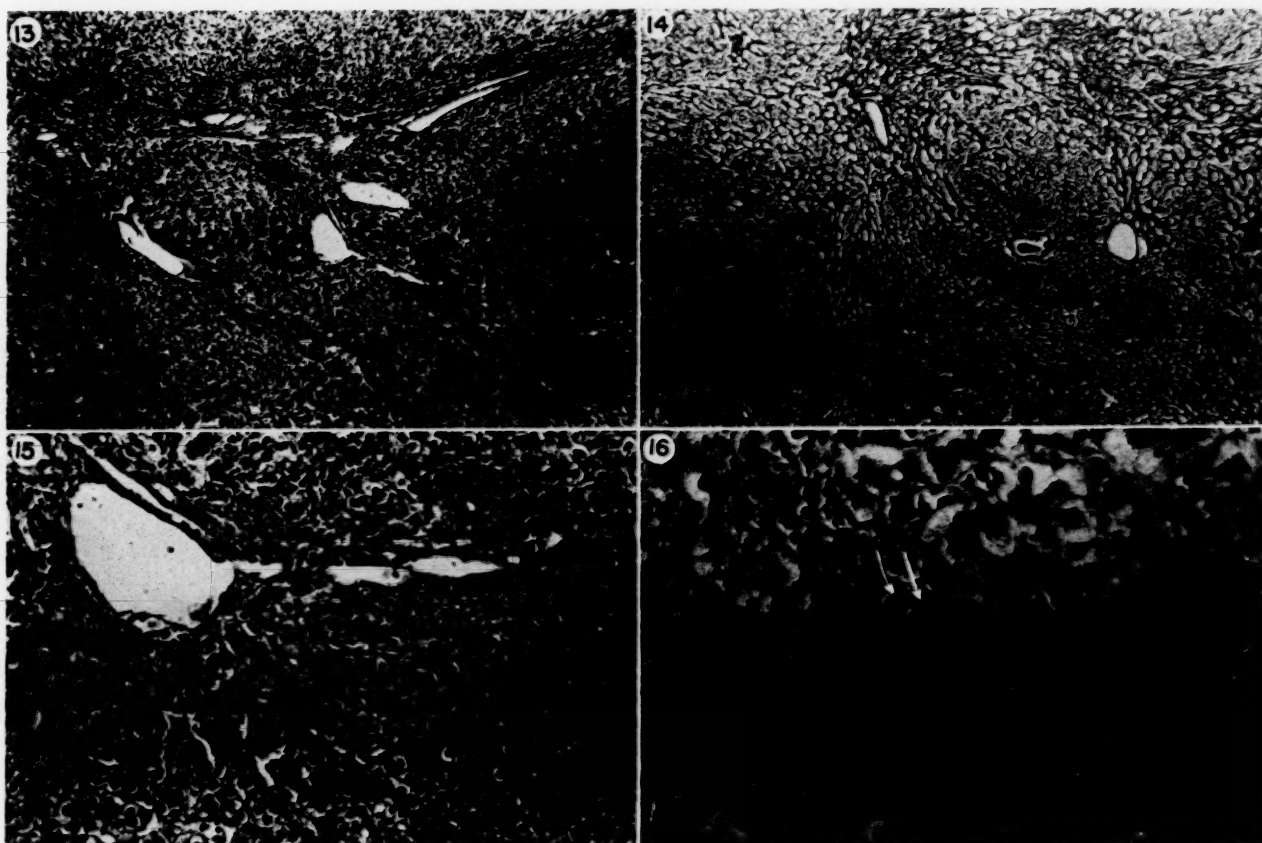


FIG. 13. Case iv. Surgical biopsy specimen of the liver obtained fourteen months after the onset of illness. Low magnification showing broad and slender areas of necrosis and collapse heavily infiltrated with mononuclear cells and bridging several portal triads and a large sublobular vein. Masson stain, original magnification  $\times 100$ .

FIG. 14. Case iv. Silver stain demonstrating the presence of collapsed reticulum fibers in the zones of necrosis illustrated in Figure 13. Laidlaw stain, original magnification  $\times 100$ .

FIG. 15. Case iv. Higher magnification of the section illustrated in Figure 13 to show pericentral necrosis. Note the absence of parenchymal cells and the presence of an intense mononuclear inflammatory reaction along the course of a slender central vein cut longitudinally as it enters a sublobular vein. Some of the parenchymal plates appear to be two-cell thick, but on cross section show a tubular arrangement (seen better in Figure 16). Masson stain, original magnification  $\times 200$ .

FIG. 16. Case iv. Cross section of two-cell thick parenchymal plates illustrated in Figure 15 to show their cylindrical structure and the arrangement of the cells in the form of rosettes. Two acidophilic bodies are seen in the center. Hematoxylin and eosin stain, original magnification  $\times 400$ .

its inception a year earlier when hyperbilirubinemia was first detected.

Following operation the patient was given a four-week course of ACTH and prednisolone. Jaundice diminished markedly, but from time to time increased and was accompanied by dark urine. The patient's appetite returned to normal and she gained weight. Steroid therapy was discontinued because of the past history of peptic ulcer and the potential hazard of hemorrhage.

When seen by me for the first time in February, 1957, three months following operation, the patient exhibited wasting, brownish pigmentation of the exposed surfaces and mild icterus of the skin and scleras. The liver edge, which was thin, soft and non-tender, was palpable 2 fingerbreadths below the

costal margin in the right mid-clavicular line, and 5 fingerbreadths below the xiphoid in the midline. No nodules were felt. A moderately firm rounded splenic tip was palpable just beneath the left costal margin, and the veins over the abdomen were prominent. However, there was no ascites or edema. The palms were erythematous but spider nevi and clubbing were absent. Liver function studies revealed gross abnormalities consistent with a severe degree of hepatocellular injury. (Table III.)

Except for persistent mild jaundice and transient episodes of pruritus, the patient felt well for the following five months during which she limited her physical activity and adhered to a high protein, low sodium diet. However, in July, 1957, she had a recrudescence of malaise and pruritus, and noted deepen-

TABLE III  
 LIVER FUNCTION TESTS IN CASE IV

Data	Date of Test					
	9/23/55	11/27/56	1/30/57	8/27/57	9/5/57	12/3/57
Serum bilirubin (mg. %):						
1-minute.....			2.19	6.48	6.04	14.9
Total.....	1.38	7.50	4.64	13.3	11.5	28.8
Bromsulphalein retention (%).....			26.5		32.6	
Cephalin-cholesterol flocculation.....	3+	4+	4+	4+	3+	4+
Thymol turbidity (units).....			14.7	12.1	3.6	18.9
Serum alkaline phosphatase (SJR units).....	9.6	8.0	27.7	16.3	13.6	34.5
Serum proteins (gm. %):						
Total.....			10.0		6.7	8.8
Albumin.....			3.0		1.8	4.1
Globulin.....			7.0		4.9	4.7
Serum cholesterol						
Total (mg. %).....			157		102	
Free (mg. %).....			69		77	
Free (%).....			44		75	
Prothrombin.....			100			
Serum glutamic-oxalacetic-transaminase (units).....			1397		246	132
Urine bile.....	1+		2+		4+	4+
Urine urobilinogen (E. units).....			0.67		0.16	0.61

ing jaundice. The urine was dark and the stools were loose but never became clay-colored. Methyl testosterone relieved the pruritus and malaise. Liver function tests a month later revealed a marked increase in the serum levels of bilirubin and glutamic-oxalacetic transaminase (Table III), suggesting further progression of the hepatic necrosis. Accordingly hospitalization was recommended.

On physical examination, the patient looked chronically ill and wasted. Her skin was moderately icteric and showed a deep brown pigmentation over the exposed surfaces. There were numerous scratch marks, but spider nevi, palmar erythema and xanthomas were not noted. A few small rubbery nodes were palpable in both posterior triangles of the neck. The heart and lungs appeared normal. Slight distention and shifting dullness were demonstrable in the abdomen, and there was an easily visible venous pattern over the anterior wall. The liver was still palpable 2 fingerbreadths below the costal margin in the right mid-clavicular line, but was much firmer and slightly tender. No nodularity was noted. The spleen was palpable 1 fingerbreadth below the costal margin. Slight edema was evident about the ankles. There was no clubbing of the fingers.

Urine analysis showed 1-plus albumin, a trace of sugar, 3-plus bile, and urobilinogen present to a dilution of 1:16. The stools were brown and guaiac-negative. Blood count showed red blood cells, 4,000,000 per cu. mm.; hemoglobin, 10 gm. per cent; hematocrit, 36 per cent; white blood cells, 5,950 per cu. mm. with

a normal differential count. The corrected sedimentation rate was 40 mm. in one hour. Liver function studies (Table III) indicated that the levels of serum bilirubin and glutamic-oxalacetic transaminase were lower than they had been one month previously, but that there had been a further decline in the serum proteins, and especially the albumin fraction, and a fall in serum cholesterol suggesting progressive destruction of the hepatic parenchyma. X-ray studies showed small esophageal and gastric varices and deformed duodenal cap with a small niche suggestive of a peptic ulcer. No evidence of decalcification of bone was found.

Needle biopsy of the liver, carried out on September 11, 1957, revealed the typical features of postnecrotic cirrhosis. In contrast to the areas of fresh collapse noted ten months previously, the septums lying between the nodules of regenerating parenchyma now consisted of dense bundles of collagen fibers infiltrated with only a moderate number of mononuclear cells, clearly indicating progression of the lesion to the stage of cirrhosis. (Fig. 17.) However, the parenchyma still showed signs of activity as indicated by the presence of pleomorphism, irregular staining, occasional acidophilic bodies, foci of reticuloendothelial hyperplasia and round cell infiltration. Many of the parenchymal cells were arranged in thick plates and tubelike structures or rosettes. (Fig. 18.)

The patient was afebrile during her eight-day stay in the hospital. On conservative therapy of bedrest, a high protein diet and salt restriction she ate well, had

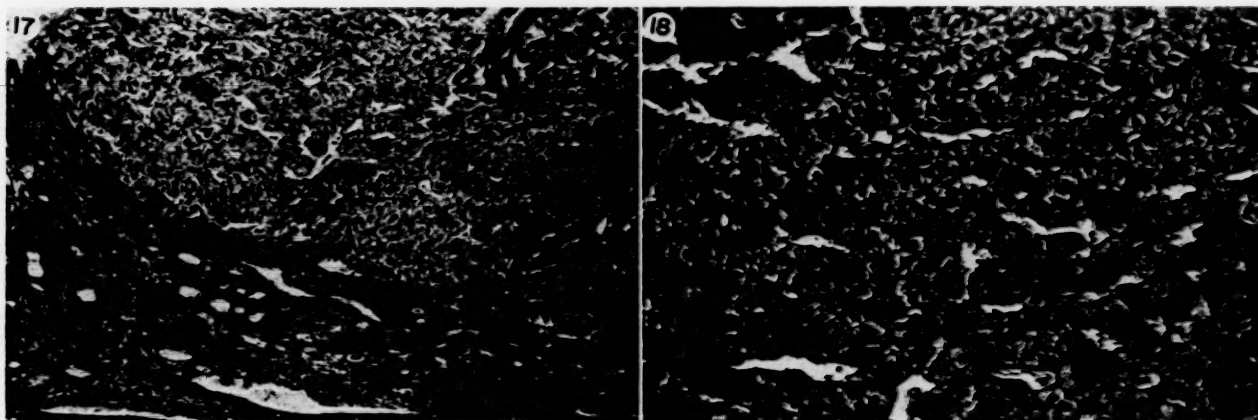


FIG. 17. Case iv. Needle biopsy specimen of liver obtained twenty-four months after the onset of illness. Edge of a large parenchymal nodule surrounded by a broad highly vascularized connective tissue septum infiltrated with many mononuclear cells. Van Gieson's stain revealed the presence of numerous thick collagen fibers in the internodular septums. Masson stain, original magnification  $\times 200$ .

FIG. 18. Case iv. Higher magnification of section illustrated in Figure 17 to show broad parenchymal plates apparently two-cell thick. In cross section it can be seen that these are cylindrical structures. Masson stain, original magnification  $\times 200$ .

no complaints and all the edema and most of the ascites disappeared. Steroids were not administered because of the presence of a peptic ulcer. Since discharge from the hospital, a period of approximately three months, the patient has felt well, but fluctuating jaundice and minimal ascites has persisted.

*Comment:* It is highly probable that the onset of hepatitis in this case occurred in September, 1955, and that the previous gastrointestinal complaints were due to an unrelated peptic ulcer. While slight hyperbilirubinemia and other laboratory evidence of hepatocellular disease were demonstrable at this time, overt jaundice did not become evident until thirteen months later. As in Case iii, the jaundice was misinterpreted as a sign of extrahepatic biliary obstruction and led to surgical exploration. Later, the chronic jaundice, brownish pigmentation, pruritus, hepatosplenomegaly and hyperphosphatasemia mimicked the picture of primary biliary cirrhosis.

#### CLINICAL FEATURES

*Age and Sex.* The preponderance of middle aged and elderly women in this group was striking. Indeed, all but one of the nine patients were women over the age of forty years. (Table iv.) Six of these were menopausal, but in three the menopause was surgically induced.

*Early Manifestations* (Table iv). A relatively abrupt onset with non-specific constitutional and gastrointestinal symptoms was characteristic.

Weakness, fatigability, abdominal pain, anorexia, indigestion, nausea and vomiting were the principal complaints, and occurred in varying combination and sequence in individual cases. Only two patients noted fever at the onset. With few exceptions, the abdominal pain was dull aching in character, intermittent and localized in the epigastrium, and often it was aggravated by the ingestion of food or by physical activity. All but two patients noted significant weight loss as the disease progressed.

The symptoms were sufficiently troublesome to induce every patient in the group to seek medical attention early in the course of the illness. In no instance was the presence of hepatocellular disease recognized, testifying to the non-specificity of the complaints. However, it is noteworthy that, despite the absence of clinically detectable jaundice, five patients noted dark urine, light stools and/or pruritus, and all four tested before the appearance of overt signs of liver disease exhibited abnormalities of hepatocellular function, features that were either misinterpreted or dismissed as insignificant.

Careful inquiry revealed only two instances of possible exposure to infection with the hepatitis virus. In Case vi the patient had been a combat soldier for an extended period in an area in which viral hepatitis was known to be prevalent; in Case vii the patient had received a large number of transfusions 30 and 163 days prior to the onset of symptoms.

Frank signs of liver disease first became appar-

TABLE IV  
INITIAL SYMPTOMS IN NINE PATIENTS WITH ANICTERIC SUBACUTE HEPATIC NECROSIS

Data	Case No.								
	I	II	III	IV	V	VI	VII	VIII	IX
Age at onset (yr.)	52	66	42	48	47	34	50	55	61
Sex	F	F	F	F	F	M	F	F	F
Menopause	+	+	0	0	+	..	+	+	+
Constitutional symptoms:									
Weakness and fatigue	0	0	0	+	+	+	+	+	0
Weight loss	0	+	0	+	+	+	+	+	+
Fever	0	0	0	0	0	0	+	0	+
Gastrointestinal symptoms:									
Anorexia	0	+	0	+	+	0	+	0	+
Nausea and/or vomiting	0	0	+	0	+	0	+	0	+
Abdominal pain	+	+	0	+	+	+	+	+	+
Indigestion	0	0	+	+	+	+	0	+	0
Hepatobiliary symptoms:									
Dark urine	+	0	+	0	0	0	0	0	+
Light stools	+	0	+	0	0	0	+	+	+
Pruritus	0	0	+	0	0	0	0	+	0
First sign of overt liver disease (mo. from onset):	3	3	4	13	4½	2	8	18	14
Jaundice	0	+	+	+	+	0	0	0	+
Hepatomegaly	0	0	0	0	0	+	+	+	0
Splenomegaly	0	0	0	0	0	+	0	0	0
Ascites	+	+	0	0	0	0	0	0	0
Bleeding esophageal varices	0	0	0	0	0	0	0	0	0

\* Surgically induced.

ent from two to eighteen months following the onset of illness. In half the group the antecedent symptoms were present more or less continuously, but four patients (Cases I, III, IV and VII) experienced one or more remissions of varying duration. The interval between the onset and the appearance of these signs was between two and eight months in six patients, and between twelve and eighteen months in three patients.

The first sign pointing to involvement of the liver was jaundice in five patients, hepatomegaly in three, and ascites in one. In Case II the jaundice was accompanied by ascites, and in Case VI hepatomegaly was accompanied by splenomegaly.

*Late Manifestations (Table v).* Although the onset was anicteric in every instance, jaundice ultimately appeared in eight of the nine cases following a preicteric phase which varied in duration from three to fifty-five months. Once jaundice became evident, it tended to persist

with only minor fluctuations. However, in three cases there were complete remissions, two occurring spontaneously (Cases I and III) and one following ACTH therapy (Case II). In Case VI jaundice appeared only terminally after an illness of fifty-five months' duration.

Dark urine was noted by all patients in whom jaundice developed. In addition, there were six patients with light stools and five with pruritus, features that were responsible for many of the diagnostic errors encountered in this group.

Considering the chronicity and the severity of the liver disease in this group, it was surprising to find that spider nevi or palmar erythema developed in only two patients. Striking dark brown pigmentation of the exposed surfaces was seen in three patients (Cases IV, VI and VIII), in one of whom it was sufficiently intense to suggest the possibility of hemochromatosis to the attending physician. None of the patients exhibited xanthomas.

TABLE V  
LATE MANIFESTATIONS IN NINE PATIENTS WITH POSTNECROTIC CIRRHOSIS FOLLOWING ANICTERIC  
SUBACUTE HEPATIC NECROSIS

Data	Case No.								
	I	II	III	IV	V	VI	VII	VIII	IX
Signs:									
Jaundice (mo. from onset) . . . . .	5	3	4	13	4½	55	..	33	14
Type* . . . . .	IT	Tr	IT	P	P	T	0	P	P
Dark urine . . . . .	+	+	+	+	+	+	0	+	+
Light stools . . . . .	+	+	+	0	+	0	0	+	+
Pruritus . . . . .	+	+	+	+	0	0	0	+	0
Hepatomegaly . . . . .	+	+	0	+	+	+	+	+	+
Splenomegaly . . . . .	+	+	0	+	0	+	+	+	+
Ascites . . . . .	+	+	+	+	+	0	0	0	0
Edema . . . . .	+	+	+	+	0	0	0	0	+
Spider nevi . . . . .	0	0	0	0	0	0	+	0	0
Palmar erythema . . . . .	+	0	0	+	0	0	0	0	0
Esophageal varices . . . . .	+	0	+	+	0	0	0	0	+
Bleeding varices . . . . .	+	0	0	0	0	0	0	0	0
Symptoms:									
Weakness and fatigue . . . . .	+	+	+	+	+	+	+	+	+
Weight loss . . . . .	+	+	+	+	+	+	+	+	+
Fever . . . . .	+	0	+	0	+	0	0	0	0
Anorexia . . . . .	+	+	+	+	+	0	+	+	+
Nausea and/or vomiting . . . . .	0	+	+	+	+	0	0	0	0
Abdominal pain . . . . .	0	+	0	0	+	+	0	+	0
Indigestion . . . . .	+	0	+	+	+	+	0	+	+

\* Tr = transient, P = persistent, I = intermittent, T = terminal.

Hepatomegaly was demonstrable at some time during the course of the disease in all but Case III. As a rule the liver was only slightly to moderately enlarged, being palpable from 1 to 3 fingerbreadths below the costal margin, but in Cases I and VIII it ultimately extended more than a handsbreadth below the costal margin. In only two patients (Cases VI and IX) was progressive diminution in the size of the liver noted. The liver edge tended to be firm in consistency, but in Cases II and VII it remained soft even late in the disease. Tenderness was not a prominent feature, being present only early in the course of the disease in four patients (Cases II, IV, V and VII). Although coarse nodules were demonstrable at operation or at autopsy in four instances, they were palpable in only one (Case I).

All but two of the patients had splenomegaly. In most instances the spleen was only slightly enlarged but in Case VI it extended a handsbreadth below the costal margin, overshadowing the accompanying hepatomegaly and leading to the incorrect diagnosis of Banti's syndrome.

Radiographic evidence of esophageal varices was found in four cases, but hemorrhage occurred in only one.

As in the preicteric phase, constitutional and gastrointestinal symptoms predominated. Without exception the patients lost weight and complained of weakness and fatigability. All but one had marked anorexia, and all but two were troubled with indigestion. Intermittent nausea and/or vomiting was present in four cases. Abdominal pain, which occurred in four patients, varied considerably in character and severity. In Case II there was a single episode of severe colicky pain in the upper right quadrant, in Case VI the patient had recurrent attacks of colicky pain in the upper left quadrant, while in Cases V and VIII there was mild postprandial epigastric aching. Three of the patients ran an intermittent low grade fever.

*Laboratory Features (Table VI).* Despite the chronicity and severity of the disease, and the frequency of splenomegaly, anemia or leukopenia developed in only two patients, and none

TABLE VI  
LABORATORY FEATURES\* IN NINE PATIENTS WITH POSTNECROTIC CIRRHOSIS FOLLOWING ANICTERIC  
SUBACUTE HEPATIC NECROSIS

Data	Case No.								
	I	II	III	IV	V	VI	VII	VIII	IX
Hemoglobin (gm. %)	13.0	14.5	11.9	11.8	12.1	14.0	13.3	13.5	14.2
	10.5	12.8	11.5	10.4	.....	12.5	9.0	13.0	12.0
Leukocytes (thousands per cu. mm.)	24.4	12.2	5.4	9.1	11.4	17.0	12.4	15.7	6.6
	4.1	9.8	5.1	5.2	8.4	5.2	5.7	12.3	3.0
Serum bilirubin, direct (mg. %)	11.7	4.2	0.4	14.9	7.0	4.3	0.5	2.3	1.1
	0.4	0.4	.....	2.2	4.2	0.3	0.1	1.4	0.7
Serum bilirubin, total (mg. %)	23.8	9.5	1.0	28.8	11.8	7.9	1.3	5.4	3.3
	1.1	0.8	.....	1.4	8.2	1.8	0.6	2.6	1.9
Bromsulphalein retention (%)†	60.5	59.3	50.6	32.6	.....	40.0	25.9	51.0	32.6
	39.5	54.6	.....	26.5	.....	27.0	6.9	40.5	22.7
Cephalin-cholesterol flocculation‡	4+	4+	4+	4+	4+	4+	4+	4+	4+
	2+	2+	0	3+	3+	3+	0	3+	0
Thymol turbidity (units)	35.0	11.8	13.5	18.9	33.6	12.5	20.3	12.5	6.3
	4.4	5.2	5.6	3.6	24.2	5.0	9.1	7.0	1.5
Serum alkaline phosphatase (SJR units)	17.8	15.1	7.7	34.5	9.6	12.5	16.2	50.5	46.1
	3.2	7.1	4.0	8.0	4.2	5.1	5.6	24.0	5.2
Serum proteins, total (gm. %)	7.4	6.0	6.4	10.0	9.2	6.9	8.0	7.2	6.8
	4.7	5.9	5.1	6.7	7.6	5.5	5.2	.....	6.4
Serum albumin (gm. %)	4.2	2.5	2.5	4.1	3.5	5.2	3.4	2.7	2.6
	1.9	2.4	.....	1.8	2.9	2.8	2.6	.....	2.5
Serum globulin (gm. %)	4.6	3.6	3.9	7.0	5.8	3.6	5.4	4.4	4.3
	2.5	3.2	.....	4.7	4.8	1.5	3.8	.....	2.5
Serum cholesterol, total (mg. %)	235	260	202	157	170	236	290	.....	214
	181	245	.....	102	.....	219	204	.....	.....
Serum free cholesterol (% of total)	35	58	37	75	42	39	33	.....	35
	34	42	.....	44	.....	27	26	.....	.....
Prothrombin (% of normal)	50	80	73	100	10	100	100	100	100
	29	26	.....	.....	10	64	62	.....	80

\* Highest and lowest values recorded for each determination.

† Retention at forty-five minutes following 5 mg./kg. dose.

‡ Read at forty-eight hours.

exhibited thrombocytopenia. Half the patients had leukocytosis at one time or another. In a few instances this was associated with hemorrhage or intercurrent infection but in several it appeared to be related to the underlying liver disease.

The serum bilirubin was elevated in eight patients. In all six cases studied during the preicteric phase or during a remission there was an increase in serum bilirubin, involving both the direct- and indirect-reacting fractions in Cases I, IV, VI and IX, and the direct-reacting fraction alone in Cases III and VII. Marked bromsulphalein retention was the rule, and only in Case VII did the level fall below 20 per cent during a remission.

At one time or another, every patient had a

4-plus cephalin-cholesterol flocculation reaction. However, it is noteworthy that the reaction was negative initially in Case VII, and became negative late in the course of the disease in Cases III and IX, despite evidence of progressive hepatic destruction. Thymol turbidity was significantly increased in all cases, exceeding 10 units in eight and 20 units in three. Although the two highest values were obtained in the sickest patients, fluctuations in thymol turbidity were not closely correlated with the clinical course. Thus progression of the disease was attended by a fall in the level in Cases I and IV, and by a rise in Cases II, VI, VIII and IX.

The serum alkaline phosphatase activity rose in all but Case III, and reached levels in the obstructive jaundice range (15.1 to 50.5 units)

TABLE VII  
DIFFERENTIAL DIAGNOSIS AND CLINICAL COURSE IN NINE PATIENTS WITH POSTNECROTIC CIRRHOSIS  
FOLLOWING ANICTERIC SUBACUTE HEPATIC NECROSIS

Case No.	Diagnoses before Biopsy	Surgical Findings (date from onset)	Complicating Disease	Clinical Course	Duration of Disease (mo.)	Cause of Death	Autopsy Findings
I	Malignancy, portal vein thrombosis, amyloidosis	.....	Rheumatoid arthritis, cholelithiasis	Intermittently progressive, fatal	48	Bleeding varices	Coarsely nodular liver, 1,000 gm.; one stone in gallbladder
II	Malignancy, common duct stone, hepatic necrosis	.....	.....	In remission	15+	.....	.....
III	Common duct stone, biliary cirrhosis	Liver "wrinkled" (4 mo.)	Gallstones removed in the past	Intermittently progressive, fatal	10	Hepatocellular failure	.....
IV	Malignancy, cholelithiasis, biliary cirrhosis	Liver enlarged, coarsely nodular (14 mo.)	Duodenal ulcer, healed	Intermittently progressive	26+	.....	.....
V	Common duct stone	Liver small, finely nodular (5½ mo.)	.....	Progressive, fatal	5½	Hepatocellular failure	Finely granular liver, 1,090 gm.; duodenal ulcer
VI	Banti's syndrome, hepatic a-v fistula, hepatic hemangioma, cirrhosis, ? type	Liver enlarged, coarsely and finely nodular (13 mo.)	Terminal appendicitis	Progressive, fatal	55	Appendicitis, peritonitis	Coarsely nodular liver, 1,470 gm.; pyelophlebitis, peritonitis
VII	Viral hepatitis, cirrhosis, ? type, malignancy, sarcoidosis	Normal liver (7 weeks)	Hereditary telangiectasia	In remission	23+	.....	.....
VIII	Hemochromatosis, malignancy, biliary cirrhosis	.....	Pneumonia	Progressive, fatal	37	Hepatocellular failure	.....
IX	Common duct stone, biliary cirrhosis, malignancy	Liver enlarged, coarsely nodular (14 mo.)	Pneumonia, cholelithiasis, arthritis, ? type	Progressive	36+	.....	.....

in six of the nine cases. Of particular interest is the fact that the serum alkaline phosphatase varied independently of the serum bilirubin concentration, and in three patients (Cases VII, VIII and IX) was markedly elevated in the absence of jaundice. Five of the six patients with levels in the obstructive jaundice range had light colored stools, and three had pruritus, a combination of features that was misinterpreted as evidence of extrahepatic biliary obstruction in several instances.

Low levels of serum albumin were a constant finding, but in four of the cases the concentration was above 3.0 gm. per cent early in the course of the disease. In general, the concentration fell as hepatocellular function deteriorated. The serum globulin concentration was above 3.5 gm. per cent in all cases, and reached levels above 4 gm. per cent in six. The three patients with globulin values over 5.0 gm. per cent had total serum protein concentrations that ranged from 7.9 to 9.8 gm. per cent. Early in the course of the illness, the globulin level tended to rise but as the disease progressed the concentration fell, often reaching normal or subnormal values.

In only one of the eight cases tested was the serum cholesterol concentration elevated, but

in five there was a significant increase in the unesterified fraction. One patient showed a progressive fall in serum cholesterol to a subnormal level as the disease progressed. Despite the evidence of severe hepatocellular dysfunction in most of the cases, in only three did significantly low levels of prothrombin develop.

*Clinical Course (Table VII).* The disease tended to run a progressive course, and was fatal in five of the nine cases after intervals ranging from five and a half to fifty-five months (average thirty-one months). All five patients died in hepatic coma following progressive hepatocellular failure, but death was precipitated by massive bleeding from esophageal varices in Case I, and by acute appendicitis and peritonitis in Case VI. As of the present writing (December, 1957) four patients are still alive fifteen to thirty-six months after onset (average twenty-five months). The disease is still actively progressive in two cases, but is quiescent in the others. The remission was spontaneous in Case VII, and was induced by steroid therapy in Case II. In three of the fatal cases there were also spontaneous remissions of several months' duration during the course of the disease.

By and large the results of treatment with a

high protein, low sodium diet, vitamin supplements, diuretics, and periods of bedrest were unsatisfactory in that weight loss, weakness and ascites were seldom adequately controlled. Three patients received courses of ACTH and/or adrenocortical steroids. In Case II, ACTH and prednisone given over a four month period induced a complete remission that has been sustained for a period of eight months. A two-week course of intravenous ACTH in Case I had little effect and was therefore interrupted. In Case IV the patient was given ACTH and prednisolone for four weeks with prompt relief of symptoms but treatment was discontinued because of the presence of a complicating peptic ulcer. Experience with several patients with the classic type of subacute hepatic necrosis seen more recently suggests that prolonged treatment with steroids may be effective in this group, particularly if instituted early in the course of the disease.

*Differential Diagnosis.* As previously noted, all the patients were seen by a physician early in the course of their illness but the presence of liver disease was not suspected until relatively late when overt signs of hepatic involvement became evident. Even then viral hepatitis and subacute hepatic necrosis were not considered diagnostic possibilities in seven of the nine cases, and in these the nature of the disease was not recognized until after liver biopsy.

Once signs of liver disease appeared, a number of diagnostic possibilities were considered. As is evident from Table VII, the principal errors in diagnosis were common duct stone, biliary cirrhosis and malignancy. In most instances it was the association of jaundice with clay-colored stools, pruritus, epigastric distress and a high serum alkaline phosphatase level that suggested cholelithiasis. In addition, one of the patients had had a cholecystectomy for a stone in the past, and two others were found to have gallstones which proved subsequently to be unrelated to the underlying illness. The fact that the obstructive-like jaundice was accompanied by hepatosplenomegaly raised the question of biliary cirrhosis of either the primary or secondary type. In more than half the cases the possibility of malignancy was given serious consideration, chiefly because of the progressive weight loss and weakness which were such prominent features. Early in the disease epigastric pain and indigestion pointed to carcinoma of the gastrointestinal tract but once jaundice and hepato-

megaly appeared, carcinoma of the pancreas, biliary tract or liver was considered more likely.

In two patients the sudden appearance of splenomegaly following an episode of epigastric pain was interpreted as evidence of portal or splenic vein thrombosis. One of these patients (Case VI) had been in a car accident and was found to have a loud bruit over the liver, which suggested the possibility of an intrahepatic arteriovenous fistula or hemangioma. However, subsequent study revealed that the bruit was due to an extensive portal collateral circulation (Cruveilhier-Baumgarten syndrome).

Except for the absence of jaundice early in the disease, the clinical and laboratory features in these patients were not unlike those in a group of forty cases of classic subacute hepatic necrosis and/or postnecrotic cirrhosis with an icteric onset. (Table I.) In the latter, the diagnosis was usually established fairly promptly, so that failure to recognize the nature of the underlying process in the present series was due in large measure to an unawareness of the fact that jaundice may be absent or only a late development in the course of this disease. This was unfortunate, since it led to unnecessary surgical exploration in five of the nine cases.

#### PATHOLOGY

The histological changes encountered in the liver are outlined in Table VIII. It will be noted that needle biopsy specimens were available for study in eight of the nine cases, surgical specimens in five, and autopsy specimens in three. In all but two instances, serial studies were possible.

The first biopsy specimen was obtained within five months of the onset of the disease in four of the nine cases, while in the remainder the interval varied from twelve to twenty-five months. It was surprising to find that the lesions in the two groups were remarkably similar. Particularly impressive was the presence in the late cases of the characteristic necrotic and inflammatory changes usually expected in early subacute hepatic necrosis, a feature that was consistent with the clinical evidence of activity of the disease at the time of biopsy. Conversely, even the earliest biopsy specimens, with one exception, showed some degree of collagen deposition. Indeed, most specimens exhibited both early and late lesions side by side, and often it was not possible to estimate the duration of the disease from the histological appearance alone.

TABLE VIII  
HISTOLOGICAL FEATURES OF THE LIVER IN NINE PATIENTS WITH ANICTERIC SUBACUTE HEPATIC NECROSIS AND/OR POSTNECROTIC CIRRHOSIS

Case No.	I			II		III		IV		V		VI			VII	VIII	IX	
Specimen*	N	N	A	N	N	S	N	S	N	S	A	N	S	A	N	N	N	S
Date†	3 mo.	4 mo.	48 mo.	4 mo.	4 mo.	4 mo.	7 mo.	14 mo.	24 mo.	5 mo.	5 mo.	14 mo.	45 mo.	55 mo.	12 mo.	25 mo.	14 mo.	14 mo.
Lobular disorganization:																		
Nodules	+++	0	+++	+++	+++	0	+++	+++	+++	+++	+++	+++	+++	+++	++	++	++	++
"Bridging"	0	++	+++	0	++	+++	++	+++	++	++	++	++	++	++	0	++	++	0
Intact portal triads	0	++	+++	0	++	+++	++	+++	++	++	++	++	++	++	++	++	++	++
Intact central veins	0	++	+++	++	++	+++	++	+++	++	++	++	++	++	++	++	++	++	++
Stroma:																		
Collapsed reticulum	++	0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Collagen	+	+	++	++	++	0	++	++	++	++	++	++	++	++	++	++	++	++
Vascularity	++	0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Cellular infiltration	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Bile duct proliferation	++	0	+	++	++	+	++	+	+	++	++	+	0	+	++	++	++	0
Parenchyma:																		
Acidophilic bodies	++	0	++	+	+	++	++	++	++	++	++	++	++	++	++	++	++	0
Other degeneration	++	0	++	0	0	0	++	0	0	++	++	++	++	++	++	++	++	++
Mitoses	0	0	0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Binucleate cells	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Thick plates	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
"Rosettes"	0	++	0	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Multinucleated giant cells	0	0	±	0	0	++	++	0	0	++	++	0	0	0	0	0	0	0
Cellular infiltration	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Reticuloendothelial hyperplasia	++	++	0	0	0	++	++	++	++	++	++	++	++	++	++	++	++	++
Granulomas	0	0	0	0	0	++	++	0	0	0	0	0	0	0	0	0	0	0
Fatty infiltration	0	0	0	0	0	0	++	0	0	0	0	0	0	0	0	0	0	0
Hemosiderin granules	0	0	0	++	++	0	++	++	++	++	++	++	++	++	++	++	++	++
Pigmented histiocytes	0	0	0	++	++	0	++	++	++	++	++	++	++	++	++	++	++	++
Bile thrombi	0	0	0	±	±	0	0	+	0	++	++	0	0	++	0	0	0	0

NOTE: ± = minimal or rare; + = slight or few; ++ = moderate; +++ = severe or numerous.

\* N = needle biopsy; S = surgical biopsy; A = autopsy specimen.

† Months from onset of illness.

In reviewing biopsy material obtained from a group of patients with classical viral hepatitis and early jaundice with progression to subacute hepatic necrosis, these same features were observed.

*Lobular Disorganization.* The outstanding finding in all specimens was the loss of parenchymal cells and collapse of the supporting stroma, resulting in distortion of the normal lobular architecture. The pattern of collapse was of two types. In one, the zones of necrosis involved whole lobules or groups of contiguous lobules, in an irregular fashion, giving rise to broad bands of collapsed stroma lying between islands of surviving parenchyma of varying size and shape. (Figs. 1, 2, 13 and 14.) As the disease progressed there was a tendency for the islands to proliferate, producing large parenchymal nodules which compressed the intervening stroma into relatively smooth, broad or slender septums. (Figs. 6, 12 and 17.) That these large nodules were derived from collections of surviving lobules was evident from the number of intact portal triads and/or central veins that could be demonstrated near their periphery. The other type of collapse was less common, and consisted of linear zones of necrosis bridging central and portal areas of adjacent lobules in a symmetrical fashion, so that the normal lobular architecture could still be discerned. (Figs. 8 and 9.) Although this type of collapse was seldom found alone in large sections of liver, its chief importance was in the study of needle biopsy specimens, since the presence of clear-cut bridging between adjacent portal triads or between portal triads and central zones almost invariably indicated the presence of subacute hepatic necrosis.

Irregular collapse and nodule formation were evident at some time during the course of the disease in every case, but in five there were, in addition, areas in which bridging predominated. Early in the course of Case III the liver showed fine diffuse bridging without nodule formation. (Figs. 8 and 9.) The liver appeared finely wrinkled at this time. However, three months later a repeat liver biopsy specimen revealed frank nodule formation. (Fig. 12.) Four of the six other livers examined at operation or at autopsy were coarsely nodular. (Fig. 5 and Table VII.) In Case V, in which the course was the most fulminant, there were large zones of necrosis with very small nodules, apparently reflecting a failure in hepatocellular regenera-

tion. (Fig. 19.) In Case VII the liver, which was inspected during the course of a surgical exploration for an unrelated condition, was found to be normal in appearance seven weeks after the apparent onset of liver disease. Unfortunately, a biopsy specimen was not obtained since the significance of the abnormalities of liver function, which appeared just prior to surgery, was not appreciated.

With only one exception (Case III), all surgical and autopsy specimens showed a broad zone of subcapsular collapse many times the normal thickness of Glisson's capsule. Often these extended deeply into the parenchyma along the normal extensions of Glisson's capsule.

*Stroma.* In the earliest lesions the septums were made up predominantly of collapsed and somewhat thickened reticulum fibers outlining numerous narrow sinusoids filled with blood and inflammatory cells. (Figs. 2, 9 and 14.) At this stage only a few of the fibers took up the van Gieson stain for collagen, and then only lightly. The fact that such fibers often appeared in areas completely devoid of fibroblasts or inflammatory cells suggested the possibility that they represented altered reticulum rather than newly deposited collagen. As the lesion aged the reticulum fibers appeared thicker and more compressed, collagen fibers became more numerous, and the meshwork of sinusoidal capillaries was gradually obliterated, although even in the oldest lesions the septums usually appeared more vascular than in other forms of cirrhosis. (Figs. 6, 7, 12, and 17.)

Early in the disease the zones of collapse showed a diffuse inflammatory reaction characterized by a predominantly mononuclear exudate made up of lymphocytes, numerous plasma cells and histiocytes, some of which occasionally contained yellowish pigment. (Figs. 3, 10, 11 and 15.) Some sections contained a moderate number of eosinophils and a small number of polymorphonuclear cells. Although the inflammatory exudate was diffusely distributed, it showed a tendency to aggregate around blood vessels and bile ducts, and occasionally formed nodules resembling lymph follicles. Often the exudate became less prominent as the disease progressed but this was not an invariable finding.

Reduplication of the fine interlobular bile ducts was evident to some extent in most sections but was especially prominent in large areas of collapse (Fig. 4), including those beneath the

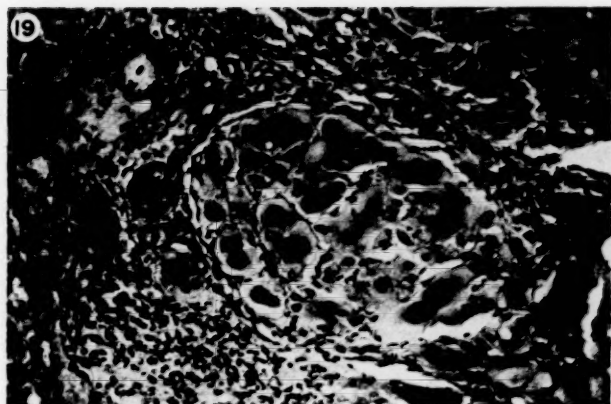


FIG. 19. Case v. Surgical biopsy specimen obtained five months after the onset of illness. Small island of multinucleated giant parenchymal cells surrounded by a large zone of recent necrosis and stromal collapse. The cytoplasmic vacuoles illustrated contain inspissated bile and iron-staining material. Hematoxylin and eosin stain, original magnification  $\times 200$ .

capsule, and was seldom seen in the long slender septums lying between nodules. No doubt the aggregation of ducts from a number of collapsed lobules contributed to their apparent increase but their tortuosity and branching indicated that proliferation was an additional important factor. As the disease progressed the ducts appeared to diminish in number, and were seldom prominent in frankly collagenized areas (Figs. 6, 12 and 17), suggesting that they were being obliterated as the fibrotic process advanced.

**Parenchyma.** In addition to the zones of collapse, representing areas of hepatocellular necrosis and dissolution, all sections showed varying degrees of degeneration, regeneration and inflammation involving the surviving parenchyma. These changes were most striking early in the course of the disease but even the oldest lesions showed them to some extent.

All but two of the seventeen specimens examined contained scattered acidophilic bodies (Councilman-like bodies), the rounded, intensely eosinophilic, homogeneous cytoplasmic masses derived from hepatic cells undergoing coagulation necrosis. (Figs. 10, 15 and 16.) Often these were found in an early stage of development and still contained remnants of a pyknotic nucleus. (Fig. 3.) These structures are a characteristic feature of viral hepatitis [2,7], although it is well recognized that they are seen occasionally in small numbers in other forms of liver disease.

Several other types of degeneration were en-

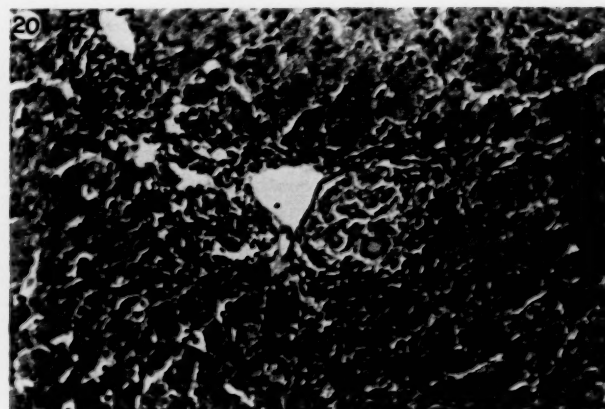


FIG. 20. Case III. Surgical biopsy specimen of liver obtained four months after onset of illness illustrating the presence of a non-specific granuloma containing numerous epithelioid cells and one giant cell in a portal triad. Hematoxylin and eosin stain, original magnification  $\times 200$ .

countered. Some cells were swollen to several times their normal size, producing so-called balloon cells (Fig. 11), some were shrunken and contained pyknotic nuclei, while others showed irregularities in cytoplasmic staining. (Figs. 3, 4, 11 and 15.)

Although mitoses were rare, there were many other features indicative of hepatocellular regeneration. These included numerous binucleate cells (Figs. 3 and 4), hyperchromatism, variations in cell size and cytoplasmic staining, and the presence of parenchymal plates appearing two cells thick. (Figs. 15, 16 and 18.) On cross section, the latter often appeared to be tubular in structure, the parenchymal cells being arranged in rosettes around a small central lumen. A few sections contained exceedingly large parenchymal cells with multiple, centrally placed nuclei. This was particularly striking in both specimens obtained from Case v, in which most of the surviving parenchyma was transformed into masses of multinucleated giant cells containing numerous bile droplets and hemosiderin granules (Fig. 19), a morphological picture reminiscent of neonatal giant cell hepatitis [17].

Scattered through the sinusoids were small collections of mononuclear cells and foci of large proliferating reticuloendothelial cells. (Figs. 11 and 16.) In Case III there were, in addition, a few small epithelioid granulomas apparently derived from the latter. (Fig. 20.)

Only two of the sections contained a few fat-filled parenchymal cells. (Fig. 12.) In both instances an earlier biopsy specimen showed none,

so that the fatty infiltration was probably unrelated to the underlying disease.

With two exceptions, routine iron stains failed to reveal any hemosiderin. In Case II a small number of iron-stained granules were found in a few of the parenchymal cells and histiocytes, while in Case V most of the previously described multinucleated parenchymal cells contained numerous coarse hemosiderin granules.

Bile thrombi were relatively infrequent. In Cases II and IV there were a few intracanalicular bile thrombi early in the course of the disease; in Case VI there was a large number terminally. In Case V there were numerous bile thrombi both in the canaliculi and within the multinucleated giant parenchymal cells. (Fig. 19.)

#### COMMENT

The cases presented clearly indicate that anicteric attacks of hepatitis are capable of producing subacute hepatic necrosis and postnecrotic cirrhosis. The question arises, however, whether or not the available evidence warrants the assumption that the hepatitis virus was the etiological factor in these cases. Certainly, unequivocal proof, which at present demands transmission of the virus to human volunteers, was not established. However, all the cases fulfilled the less rigid clinical, biochemical and histological criteria usually considered acceptable evidence of specific infection, so that the etiological diagnosis in this group would appear to rest on as firm a basis as it ever does in viral hepatitis, except for the rare instances in which the infection is transmitted to human volunteers. Under some circumstances epidemiological evidence may lend support to the presumptive diagnosis of viral hepatitis, but in sporadic cases the frequency with which a history of exposure to infection can be obtained is seldom greater than it was in the present series, namely in two of nine cases.

In comparing the clinical, laboratory and histological features in the present series with those described in classic subacute hepatic necrosis with jaundice due to the hepatitis virus [8], the only consistent difference was the duration of the preicteric phase. Thus, in not one of the 125 cases reported by Lucké [8] was there a preicteric phase longer than seventeen days, and in our own series of forty cases (Table I) the maximum was thirty-one days. In contrast, the interval between the onset of illness and the appearance of jaundice in the cases under dis-

cussion ranged from three to fifty-five months, and in one instance jaundice failed to develop during the twenty-four month period of observation. This raises the question whether jaundice is a *sine qua non* of viral subacute hepatic necrosis, and whether its appearance late in the course of the disease excludes a viral etiology. Of particular interest in this connection are the Scandinavian reports [3,4,12] on an epidemic form of subacute hepatic necrosis affecting postmenopausal women. A high proportion of these patients had a long preicteric phase, and in a significant number jaundice failed to develop. In Jersild's series of 123 cases [3] the interval was greater than four weeks in 64 per cent, and 5 per cent were anicteric. As in the present series, no attempt was made to transmit the disease to human volunteers, but on the basis of epidemiological, clinical and morphological evidence it was assumed that the hepatitis virus was the responsible agent. The possibility of a strain difference or a modifying endocrine factor was postulated to account for the unusual age and sex distribution and the high mortality in this group. Other reports [5,13] concerned with sporadic cases of subacute hepatic necrosis and postnecrotic cirrhosis of presumed viral origin have also stressed the frequency with which an anicteric onset is seen. It is evident, therefore, that jaundice is not an invariable manifestation of the disease, and that when it does appear, it may do so early, as in most cases of benign infectious hepatitis, or only after a long delay, as in the present series. There is reason to believe that it is the amount of functioning parenchyma, and not the underlying etiological factor, that determines whether or not jaundice develops during an attack of subacute hepatic necrosis. Apparently hepatocellular regeneration proceeds at a sufficiently rapid rate in some cases to compensate for the expected decrease in bilirubin excretion that usually attends extensive destruction of the liver. However, once necrosis outstrips regeneration, which may occur after a variable interval on one or more occasions, jaundice appears.

As in the present series and in the epidemic form of the disease [3,4,12], women have predominated in most other reports of subacute hepatic necrosis and postnecrotic cirrhosis of presumed viral [10] or unknown [1,14] etiology. In Kelsall, Stewart and Witts' series [15], the sex distribution was equal in cases with an acute icteric onset, but in those with an insidious

anicteric onset women outnumbered men nearly three to one. Ratnoff and Patek [7], the only other authors to comment on this point, did not observe this difference. However, in our own experience with sixty-three cases of subacute hepatic necrosis and postnecrotic cirrhosis of presumed viral etiology (Table 1), males comprised 82 per cent of the group with an acute icteric onset, while females made up 74 per cent of those with an acute or insidious onset without jaundice. A similar but less striking difference in sex distribution is to be noted in the series reported by Saint and his associates [13]. It is of interest in this connection to recall that in the group of 125 cases of viral subacute hepatic necrosis collected by Lucké [8] at the Army Medical Museum, and, hence, made up almost exclusively of males, there was not one instance of an anicteric onset, the longest preicteric interval being seventeen days. Obviously further data are needed to establish whether or not there is any significant difference in the susceptibility of the sexes to the icteric form of subacute hepatic necrosis. However, it is clear from the evidence available that females predominate in the type characterized by an anicteric or insidious onset. The occurrence of both icteric and anicteric cases in epidemics of the disease involving women almost exclusively [3] makes it highly improbable that the two forms of the disease are due to different agents, one of which affects women more than men. A more plausible interpretation is that the host response to infection is different in the icteric and non-icteric groups. Although the wider distribution and the more progressive character of the lesions, as compared with those in benign viral hepatitis, suggest that in both forms of subacute hepatic necrosis the defense mechanisms are incapable of coping with the infection, due either to an inadequate immunological response or to the presence of some as yet unidentified complicating factor, it is conceivable that the less explosive character of the clinical manifestations in the anicteric form of the disease may be indicative of a greater resistance to injury, or of a better regenerative response on the part of the liver itself. This interpretation is consistent with the observation that female rats are more resistant to the hepatotoxic effects of carbon tetrachloride than males [16]. Despite the equal, or predominantly male, sex distribution in the icteric form of the disease in some studies [8,15], the occurrence of subacute hepatic necrosis in epidemics involving

females almost exclusively strongly suggests that, in addition to their tendency to respond without jaundice, women are also peculiarly susceptible to the more florid form of viral hepatitis. Further evidence of this is seen in the high mortality rate encountered in both epidemic [17] and sporadic [18] infections involving pregnant women. It is difficult to discern any common denominator in the endocrine, metabolic or nutritional pattern to account for the apparent vulnerability of women at the child-bearing age and earlier [13], during pregnancy [17], and in the menopause [3], so that no reasonable interpretation for this phenomenon can be given at the present time.

In the present report and in others in which subacute hepatic necrosis and postnecrotic cirrhosis have been attributed to the hepatitis virus [10,13], great emphasis has been laid on the morphological changes in the liver as evidence of specific infection. Confidence in the reliability of such diagnostic criteria is based on the fact that early in the infection the hepatitis virus produces characteristic histological alterations in the liver that have not been encountered in any other disease. Later, when inflammation and necrosis have subsided, and healing has occurred, the lesion is indistinguishable from that of postnecrotic cirrhosis due to other causes. In the present series biopsy material was obtained sufficiently early to demonstrate the characteristic histological features of viral hepatitis. In addition, each patient had a relatively acute onset of illness consistent with an attack of viral hepatitis, and in each case other etiological factors were excluded insofar as possible. During the same period of observation fourteen other cases were encountered, two of them acute and twelve with an insidious anicteric onset, in which the morphological picture was that of well healed postnecrotic cirrhosis. The etiology in these cases was uncertain but the resemblance to the cases under consideration was so close that a viral origin appeared probable.

The role of alcohol in the pathogenesis of postnecrotic cirrhosis and the differentiation between postnecrotic and Laennec's cirrhosis are two questions that merit consideration in any discussion of the hepatitis virus as an etiological factor in cirrhosis. In approaching this problem one is at once faced with a confusing nomenclature which has contributed to the controversy in this area. Unfortunately, it is difficult to

define Laennec's cirrhosis in universally acceptable terms, since currently it is variously interpreted as (1) a morphological entity of varied etiology with a characteristic pattern of diffuse fibrosis and fine nodule formation, (2) a form of liver disease specifically due to chronic alcoholism and/or malnutrition, and (3) a type of cirrhosis in which fatty infiltration of the liver due to any one of a number of causes, including chronic alcoholism and malnutrition, appears to be the forerunner, if not the immediate cause, of diffuse hepatic fibrosis and nodule formation. To add to the confusion, the terms portal, atrophic, fatty, alcoholic and nutritional cirrhosis, which in many instances are either inaccurate anatomically or too restrictive etiologically, are used interchangeably with Laennec's cirrhosis. In the present discussion the term is used in its most widely understood sense, namely, a form of cirrhosis usually related to chronic alcoholism and/or malnutrition but possibly due to other causes, in the pathogenesis of which fatty infiltration appears to play an important role.

Nomenclature is no less a problem in the case of postnecrotic cirrhosis of viral origin. While subacute hepatic necrosis, and its less accurate synonym subacute yellow atrophy, refer to the lesions seen early in the disease when necrosis, inflammation and stromal collapse are dominant features, the term is often used [3,4,14] to embrace the more advanced lesion characterized by fibrosis and nodule formation. Although this would appear to be a matter of little consequence, particularly since the transition is a gradual one making the line of demarcation difficult to define, it has tended to obscure the fact that the end-stage is a form of postnecrotic cirrhosis, and, indeed, to lend support to the view that the hepatitis virus does not produce cirrhosis [8], a conclusion contradicted by a wealth of clinical and pathological evidence [10,13,19-21]. It may be pointed out in this connection that Lucké, one of the authors to question the relationship between viral hepatitis and cirrhosis, based this opinion on his experience with autopsy material obtained from patients who died at a relatively early stage of subacute hepatic necrosis before fibrosis became evident [8], and on autopsy and biopsy studies in a very small number of patients with the benign form of viral hepatitis [22].

Another difficulty arises from the assumption that the liver in postnecrotic cirrhosis is in-

variably coarsely nodular. It is well known that the nodules in posthepatic cirrhosis may range in size from that of a whole lobe to small granules [10]. Baggenstoss and Stauffer [10] have found that the granular type is more common in the aged, and hence suggest that it may be indicative of a poor regenerative response. However, in our own experience the distribution and size of the zones of necrosis in the early phase of the disease have appeared to be important factors in determining the character of the nodules, granular cirrhosis being most common when the zones of necrosis have been linear in character and symmetrically distributed, bridging but not completely destroying masses of contiguous lobules. Whatever the factors are that govern nodule size, the fundamental process of acute necrosis that leads to the development of postnecrotic cirrhosis is essentially the same in all cases. For that reason the term postnecrotic cirrhosis would appear to be an appropriate designation for both coarsely nodular and finely granular forms of the disease. Some authors [13,23] use the term chronic hepatitis to describe subacute hepatic necrosis and postnecrotic cirrhosis of viral origin. This is an unfortunate practice, since the same term is commonly used [24] to indicate any form of protracted viral hepatitis, without implying any specific underlying pathological picture.

That some patients with the characteristic morphological features of postnecrotic cirrhosis have an antecedent history of chronic alcoholism and malnutrition appears to be well documented [1]. However, there is no convincing evidence to show that either of these factors produces postnecrotic cirrhosis in man. Both in man [25,26] and in experimental animals [27] chronic alcoholism and malnutrition characteristically give rise to fatty infiltration and a type of diffuse fibrosis that bears little resemblance to the changes in classic coarsely nodular postnecrotic cirrhosis. In addition, the lesions in man often show degenerative and inflammatory changes [28] which are quite unlike those seen in postnecrotic cirrhosis. Under very special dietary conditions, which require the omission of sulfhydryl-containing amino acids, tocopherol and a factor present in casein, now known to be selenium [29], it is possible to produce subacute hepatic necrosis and a postnecrotic type of cirrhosis in rats [30-32]. However, there is no evidence that these rigid dietary requirements have ever been duplicated in man, or that the

human liver is susceptible to massive necrosis under such dietary conditions. If anicteric infections with the hepatitis virus can give rise to cirrhosis, as seems probable from the evidence previously cited, it is difficult to exclude the possibility of such infection in alcoholic subjects in whom postnecrotic cirrhosis develops. Certainly when other etiological factors can be excluded, and particularly when there is a history of antecedent jaundice consistent with an attack of acute hepatitis, it is more reasonable to implicate the hepatitis virus than the coincidental chronic alcoholism and malnutrition. In our own series of sixty-three cases of postnecrotic cirrhosis of presumed viral etiology (Table 1) there were ten alcoholic patients, six of whom had a history of antecedent hepatitis with jaundice. In the remaining four with an insidious anicteric onset the livers were also coarsely nodular, and showed none of the features suggestive of Laennec's cirrhosis. Since other etiological factors were excluded, a viral etiology seemed highly probable.

The coarsely nodular type of postnecrotic cirrhosis is readily differentiated from Laennec's cirrhosis on the basis of well established morphological criteria [10]. However, it may be difficult if not impossible to distinguish between the finely granular type of postnecrotic cirrhosis and Laennec's cirrhosis, particularly in the late stages. Early in the disease the liver shows the distinctive inflammatory and necrotic changes of viral hepatitis in the former, and fatty infiltration and characteristic degenerative changes in the latter, but as the lesions heal the two pictures merge and ultimately become indistinguishable [10]. In one series of 106 selected cirrhotic livers reviewed by a panel of expert pathologists it was found that the differentiation between postnecrotic and Laennec's cirrhosis could be made on histological grounds alone in 66 per cent [33]. It is obvious, therefore, that in a considerable fraction of cases the differentiation cannot be made on morphological grounds alone. This may account for the significant number of patients with alleged Laennec's cirrhosis in whom no history of chronic alcoholism and malnutrition can be obtained [34], and in whom a viral etiology has been postulated [35]. In this connection it must be pointed out that, even when the morphological picture is typical of postnecrotic cirrhosis, it is not possible to establish a viral etiology unless the characteristic histological features of viral hepatitis, which

are seen only early in the disease, are still demonstrable. However, if other known causes of postnecrotic cirrhosis can be excluded, and particularly if a history of acute hepatitis can be obtained, a presumptive diagnosis of posthepatic cirrhosis would appear to be justified.

Of interest in the present series of cases was the frequency with which an obstructive-like jaundice ultimately developed. The clinical and laboratory features suggested some type of biliary cirrhosis and, except for the absence of jaundice early in the disease, closely resembled those in the syndrome of cholangiolitic cirrhosis described by Watson and Hoffbauer [36]. The histological evidence presented in this report confirms the view expressed by these authors that the disease probably is due to the hepatitis virus. Moreover, the age and sex incidence, and the frequency of chronic jaundice, pruritus, hyperpigmentation, hyperglobulinemia and high levels of thymol turbidity in this group are consistent with Watson and Hoffbauer's suggestion that cholangiolitic cirrhosis represents at least one form of idiopathic or primary biliary cirrhosis [37]. Xanthomatosis and hypercholesterolemia were not present in any of our cases but are not an invariable finding in primary biliary cirrhosis [37]. According to MacMahon [38], the histological features in primary or, to use his terminology, "pericholangiolitic" biliary cirrhosis are highly characteristic, and unlike those seen in the type of "cholangitic" biliary cirrhosis due to the hepatitis virus or other infectious agents. Although other pathologists appear not to have made this distinction, there is no reason to doubt that the clinical entity known as "idiopathic" or "primary" biliary cirrhosis may be due to a variety of etiological factors, some of which are still unknown. Indeed, it has been described not only as a complication of viral hepatitis [36] but also as a manifestation of hypersensitivity to a variety of drugs [39,40].

In many respects the form of chronic liver disease of young women described by Bearn, Kunkel and Slater [41] resembles the type of subacute hepatic necrosis and postnecrotic cirrhosis under consideration. Characteristically, the former attacks young girls at or near puberty, although a few women and males have been affected. Usually the onset is insidious, but in seven of the twenty-six cases reported it was consistent with an attack of viral hepatitis. In all cases examined the liver has shown the classic picture of a postnecrotic type of cirrhosis and,

although the authors make no comment on this point, the histological features described and illustrated in their paper are consistent with, if not typical of, the lesion produced by the hepatitis virus. Great emphasis has been laid on the age and sex incidence, and the frequent occurrence of amenorrhea or delayed menstruation at the onset, arthritis, recurrent bouts of fever, and extreme hyperglobulinemia predominantly involving the gamma fraction as features distinguishing this disease from other forms of cirrhosis. However, the authors recognize that similar manifestations have been observed in posthepatic cirrhosis, and admit that the hepatitis virus may be the etiological factor, although its effects on the liver may be modified by the altered endocrine status in such patients. Considering the fact that essentially the same clinical and pathological findings have been described in females at puberty and earlier [13,47], in the first four decades [10,13], and after the menopause [3,4,12], and that no convincing evidence has been presented to show that the disease is fundamentally different, either clinically, etiologically or morphologically, in each of these groups, there would appear to be no sound reason, at the present time at least, for distinguishing between them. Admittedly this opinion may have to be revised if and when specific immunological or cultural methods for the identification of the hepatitis virus become available. Bearn, Kunkel and Slater's observations [47] serve to emphasize the previously noted tendency for the anicteric form of subacute hepatic necrosis to develop in females, and their hypothesis that an endocrine factor may modify the effects of the hepatitis virus is in accord with the suggestion made in the present report that the host response to infection may be different in females.

The frequency with which the hepatitis virus produces cirrhosis is uncertain. In cases of classic hepatitis with jaundice affecting young healthy males, large scale surveys [42,43], based on clinical and laboratory criteria, suggest that cirrhosis is a rare sequela. However, even in this very select group cirrhosis may escape detection in studies that do not include liver biopsy, particularly in those cases in which there is a prolonged latent period between the initial attack of hepatitis and the appearance of frank signs of chronic liver disease [35,44]. Moreover, such surveys do not take into account the previously discussed greater susceptibility of females to

the more severe form of the disease known to produce cirrhosis, or the possibility that anicteric infections may be an important cause of this disease. In the absence of any specific diagnostic test, the number of instances in which the relationship between anicteric hepatitis and cirrhosis has been demonstrated has of necessity been small, being limited to cases encountered in epidemics [3], or to sporadic cases such as those in the present series in which biopsy material has been obtained early in the course of the disease. However, the frequent occurrence of otherwise unexplained postnecrotic cirrhosis with an insidious onset, in which the morphological features are indistinguishable from those of proved cases, suggests that anicteric infections may constitute a more important cause of cirrhosis than is indicated by the small number in which the relationship has been established. Considering the fact that the cirrhosis produced by the hepatitis virus is not always of the coarsely nodular variety, the possibility of a viral origin must also be considered in cases of finely granular cirrhosis in which no other etiological factor is evident.

#### SUMMARY

Nine cases of subacute hepatic necrosis with progression to postnecrotic cirrhosis are described in which the disease appeared to have its inception in an attack of anicteric viral hepatitis. In each instance biopsy material was obtained sufficiently early in the course of the disease to demonstrate the histological features usually considered diagnostic of the infection.

With one exception, all the patients were middle-aged or elderly women. Characteristically, the onset was relatively abrupt, with non-specific constitutional and gastrointestinal complaints, but was followed within a period of two to eighteen months by the appearance of frank signs of chronic liver disease. Jaundice was a late development in eight of the nine cases, becoming evident in three to fifty-five months from the onset. Often it was accompanied by dark urine, light stools, pruritus and hyperphosphatasemia, features that frequently were misinterpreted as evidence of extrahepatic biliary obstruction. In addition to the hyperphosphatasemia, marked hyperglobulinemia and high levels of thymol turbidity were helpful diagnostic clues. The disease tended to run an intermittently progressive course that was little

affected by dietary measures and bedrest, and terminated fatally in five of the nine cases.

Evidence is reviewed to show that females at all ages are peculiarly susceptible to the anicteric form of viral hepatitis that produces subacute hepatic necrosis and postnecrotic cirrhosis. The suggestion is made that such infections, which are readily overlooked or misinterpreted, may be responsible for many instances of otherwise unexplained cirrhosis, and particularly those of the classic postnecrotic variety that occur in females.

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# A Controlled Study of the Effects of L-Arginine on Hepatic Encephalopathy\*

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IN 1956 a series of reports by Gullino, Greenstein, du Ruisseau and co-workers [1-3] indicated that L-arginine administered parenterally protected rats against toxic doses of mixed amino acids or ammonium acetate. Since blood ammonium levels were lower and blood urea levels higher in the protected animals than in the control subjects, these workers concluded that arginine exerted its effect through stimulation of the Krebs ornithine-citrulline-arginine urea cycle. Some protective effect could be demonstrated against ammonium acetate with L-ornithine and L-citrulline as well as with L-arginine.

Najarian and Harper noted markedly increased blood ammonium ( $\text{NH}_4$ ) levels after the intravenous infusion of glycine in a dog [4]. L-arginine given concomitantly appeared to prevent the expected rise in blood  $\text{NH}_4$  and when L-arginine was administered after an elevated  $\text{NH}_4$  level had been achieved, the latter fell towards normal.

These observations have stimulated interest in the possible value of L-arginine in treatment of the encephalopathic state often associated with hepatic failure in man. Although the exact role of ammonium toxicity in this condition has not been established, it is generally agreed that circulating blood  $\text{NH}_4$  levels are higher than normal in most patients demonstrating hepatic encephalopathy [5]. Encouraging reports regarding the use of arginine in man have already been published. Bessman, Shear and Fitzgerald administered a combination of ammonium chloride and L-arginine intravenously and found that, in two patients with cirrhosis, toxic symptoms were fewer and the rise in blood  $\text{NH}_4$  was less than when ammonium chloride was given alone [6]. Najarian and Harper studied the effects of L-arginine infusion in fifteen patients

with hepatic encephalopathy and reported that clinical improvement as well as lowering of the blood  $\text{NH}_4$  level resulted in every case [7]. McDermott, Henneman and Laumont reported that arginine infusion in ten patients with encephalopathy resulted in a steady fall in blood  $\text{NH}_4$  and clinical improvement beginning twelve to twenty-four hours after the infusion [19].

The often unpredictable clinical course of patients with hepatic encephalopathy makes evaluation of therapy difficult without the use of control subjects. The current confused status of glutamate therapy in this condition is an example of the need for controlled work. Initial enthusiasm [8,9] has been followed by pessimistic reports [10,11]. Glutamate is still widely used and recommended [12] although in the single controlled study of which we are aware its value could not be confirmed [13]. We have therefore attempted to make an objective evaluation of arginine therapy in hepatic encephalopathy by means of the double blind technic, using 5 per cent glucose in water as the placebo solution.

## CASE MATERIAL AND METHODS

This study consisted of thirty-two patients from the wards of the Los Angeles County Hospital. The majority (twenty-nine) had alcoholic cirrhosis. In twenty-three of these patients encephalopathy developed in conjunction with other evidences of progression of their disease, such as jaundice and ascites. In two patients with alcoholic cirrhosis, encephalopathy followed gastrointestinal bleeding; in one it developed after paracentesis; and in two it was episodic in nature and followed a portacaval shunt. One of the latter subjects had been given ammonium chloride immediately prior to the "episode" reported herein. Three patients did not have alcoholic cirrhosis and their encephalopathy occurred in the course of biliary cirrhosis, advanced congestive cirrhosis, and

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multiple hepatic abscesses, respectively. Nine of thirty-two patients recovered sufficiently to be discharged from the hospital. The remainder eventually died.

At the onset of therapy the degree of encephalopathy varied widely from the presence of a flapping tremor and minimal disorientation to deep coma with flaccidity.

*Manner of Control of the Observations.* Thirty gm. of L-arginine hydrochloride in 500 cc. of distilled water\* served as the treatment solution and 500 cc. of 5 per cent glucose in water in an identical bottle was used as the control. The material was administered intravenously during a period of approximately two hours. One of the investigators (A. G. R.), who did not know the contents of the infusion bottle, was responsible for evaluating the patient's condition immediately before and after the infusion and again the following morning. Evaluation was concerned with such factors as the state of consciousness, the degree of orientation, the presence and severity of flapping tremor, and the ability to calculate and to write. Electroencephalograms were not obtained.

We planned to administer both arginine and the control solution to as many patients as possible, but in several instances this was not done because of the patient's marked improvement or rapid death. Twenty-two of the patients did receive both L-arginine and 5 per cent glucose. The order of administration of the two solutions was alternated.

In virtually no instance in this study was arginine or glucose solution the sole therapeutic agent used for hepatic insufficiency. No attempt was made to exclude concomitant measures. Fortunately, a more or less standard regimen is used throughout the hospital for hepatic coma, consisting of parenteral glucose, restriction of protein, oral neomycin and cathartics. The majority of our patients were treated in this fashion in addition to receiving L-arginine or the control solution.

In most patients blood was obtained from the femoral artery for measurement of ammonium levels immediately before and again after the infusions. Ammonium was determined by a slight modification [14] of the method of Seligson [15]. Blood was transferred from the collecting syringe to an oxalated tube under oil and then, using a calibrated syringe, duplicate samples were placed in the penicillin bottles. This portion of the procedure was accomplished at the patient's bedside and ordinarily required from two to four minutes. Normal values for blood ammonium nitrogen by this method in our laboratory range from 30 to 90  $\mu\text{g.}/100\text{ ml.}$  From analysis of the variation between duplicate samples, our range of accuracy is approximately  $\pm 8$  per cent. Results are therefore rounded off to the appropriate significant figure.

\* Kindly provided by Don Baxter, Inc., Glendale, California.

## RESULTS

For purposes of classification, four grades of encephalopathy were arbitrarily defined, as follows: grade 1, flapping tremor with little or no disorientation or confusion; grade 2, flapping tremor with confusion and disorientation and mild or moderate lethargy; grade 3, a semistuporous state with or without demonstrable tremor; and grade 4, deep coma with flaccidity. There is, of course, room for considerable variation in condition within these grades, particularly in grade 2. In evaluating the results of therapy, marked improvement was defined as reversion to a lesser grade of encephalopathy as herein defined. Any improvement that was recognizable but insufficient to result in a lower grade classification was called minimal or moderate.

Infusions of either glucose or arginine were given on sixty occasions to the thirty-two patients. Prior to the infusion the encephalopathy was classified as grade 1 in intensity in three instances, grade 2 in thirty-one instances, grade 3 in six instances, and grade 4 in ten instances. Thus all grades of severity of encephalopathy are represented in the study.

L-arginine was administered thirty-four times to thirty-one patients. Marked improvement occurred on two occasions (5.9 per cent); minimal or moderate improvement was noted eight times (23.5 per cent); there was no detectable change on eighteen occasions (53 per cent); and six times (17.6 per cent) the patients became definitely worse. (Fig. 1.) On evaluation the following morning one of the two patients who had shown marked improvement maintained it and one relapsed to his former condition. Three additional patients who had shown only minimal improvement after their arginine infusion appeared considerably improved the next morning.

The mean arterial ammonium level was 180 ( $\pm 19.5$ )\*  $\mu\text{g.}/100\text{ ml.}$  before administration of arginine in the twenty-five patients in whom it was measured and 160 ( $\pm 11.9$ )  $\mu\text{g.}/100\text{ ml.}$  after administration of arginine. The observed difference between these two means is less than the standard error of the difference (22.9); therefore the statistical significance of the observed fall in  $\text{NH}_4$  level cannot be established.

The control solution of 5 per cent glucose in water was administered twenty-six times to

\* Standard error of the mean.

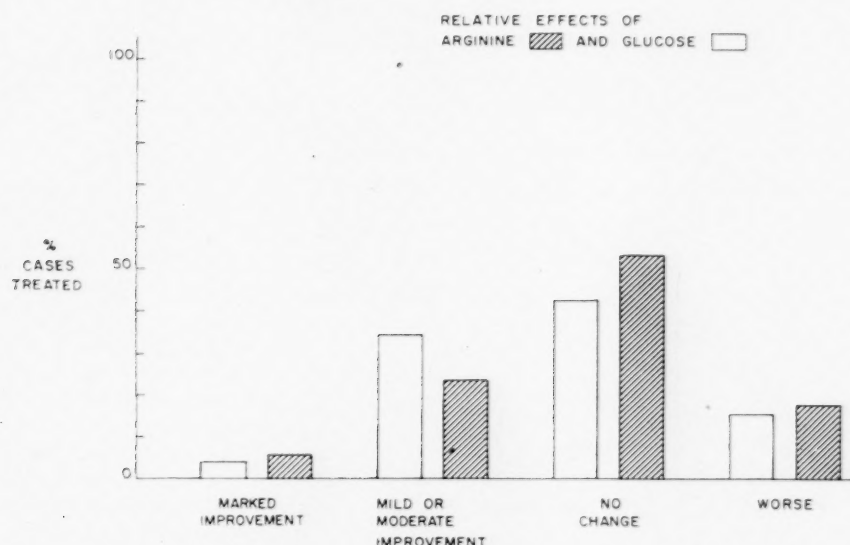


FIG. 1. Relative effects of L-arginine and glucose solutions on hepatic encephalopathy.

twenty-three patients. Marked improvement occurred in one instance (3.9 per cent) and mild to moderate improvement was seen in nine patients (34.6 per cent). No change was detectable on twelve occasions (46.6 per cent) and four times (15.4 per cent) the patients became worse. (Fig. 1.) On evaluation the next morning the patient who showed marked improvement after glucose maintained his improvement, and three additional patients appeared markedly improved over their condition the previous day. The mean arterial  $\text{NH}_4$  level was  $174 (\pm 20.7)$   $\mu\text{g.}/100$  ml. before the control solution and  $164 (\pm 20.7)$   $\mu\text{g.}/100$  ml. after it. The difference between these two means is not statistically significant.

Table 1 contains data regarding the fifteen patients who showed any improvement either with arginine or glucose. To conserve space the seventeen patients who failed to improve or who became worse are not included in the table. Patients A. F. and T. O. improved markedly after arginine. Patient A. F. relapsed to a semi-stuporous state the following day and then improved dramatically again four days later without receiving specific therapy. Patient T. O. entered the hospital in a deep stupor and manifested rapid and progressive improvement beginning the morning after hospitalization (she received arginine on this day). In T. O. the genesis of the encephalopathy remains undetermined. Patient J. R. improved markedly during the last of three glucose infusions. His response

is illustrated in Figure 2 and will be discussed subsequently.

Our conclusion from these data was that the L-arginine was no more effective than the control solution of 5 per cent glucose in the treatment of hepatic encephalopathy. A slightly higher percentage of patients showed marked improvement within the first twenty-four hours after arginine than after glucose; however, minimal to moderate improvement was seen more frequently after glucose. Arginine appeared to cause a small drop in the arterial  $\text{NH}_4$  level that could not be statistically confirmed.

#### COMMENTS

The difficulties involved in evaluating any agent in the treatment of hepatic pre-coma and coma become increasingly evident as experience with this condition increases. Occasional unpredictable recoveries occur in patients who seem terminally ill. Patients who have chronic recurrent encephalopathy after portacaval shunt may pass into deep coma for no reason that can be discerned and may recover as inexplicably. If ammonium chloride administration is the cause of encephalopathy its withdrawal will usually be accompanied by rapid improvement which might be ascribed to whatever therapeutic regimen is in use. Patients who manifest encephalopathy after gastrointestinal bleeding may undergo rapid deterioration if further (and sometimes unnoticed) bleeding occurs. In this

TABLE I  
CLINICAL DATA ON PATIENTS WHO SHOWED SOME IMPROVEMENT WHEN TREATED WITH L-ARGININE  
OR GLUCOSE

Patient and Disorder	Date and Treatment *	State of Encephalopathy before and after Treatment	Arterial NH <sub>4</sub> before and after Treatment (μg./100 ml.)	Clinical Course
H. F., thirty-six year old woman: alcoholic cirrhosis with jaundice	10/20/56 G	Grade 2	...	Flapping tremor and moderate disorientation were present; no obvious change followed either glucose infusion but there was thought to be less disorientation following the arginine infusion on 10/23; her condition began to deteriorate on 10/26 and she died in deep coma on 10/30/56
		No change	...	
	10/21/56 G	Grade 2	...	
		No change	...	
	10/23/56 A	Grade 2	...	
		Improved 1+	...	
J. A., sixty-one year old man: alcoholic cirrhosis with episodic encephalopathy, following a portacaval shunt performed 1/5/56	1/18/57 A	Grade 2	170	Periodic encephalopathy manifested by confusion and gross flapping tremor had been noted since the portacaval shunt; an unusually severe attack occasioned this hospitalization; improvement in tremor and ability to write followed the first two infusions but no change was noted after the third; discharged on 1/31, mildly improved as compared to date of entry
		Improved 1+	220	
	1/28/57 G	Grade 1 to 2	220	
		Improved 2+	150	
	1/29/57 A	Grade 1 to 2	210	
		No change	170	
J. R., fifty-five year old man: alcoholic cirrhosis; a portacaval shunt was performed in 12/55 and recurrent episodes of encephalopathy began nine months later; the present attack followed NH <sub>4</sub> Cl ingestion	1/18/57 G	Grade 2	210	Encephalopathy, manifested by gross tremor, untidiness and disorientation appeared on 1/17 after ingestion of NH <sub>4</sub> Cl for three days; although NH <sub>4</sub> Cl was discontinued on 1/17 the encephalopathic behavior continued; some improvement in orientation and ability to write was noted after the first glucose infusion; following the arginine on 1/21 he seemed more lethargic and confused; minimal improvement both in orientation and degree of tremor was recorded after the infusions of glucose and arginine on 1/22 and 1/23; marked improvement occurred on 1/25 with loss of all abnormal signs except minimal tremor; the improvement was maintained on 1/26 and he was discharged
		Improved 1+	250	
	1/21/57 A	Grade 2	220	
		Worse 2+	140	
	1/22/57 G	Grade 3	180	
		Improved 1+	70	
	1/23/57 A	Grade 2	120	
		Improved 1+	80	
	1/25/57 G	Grade 2	80	
		Improved 3+	100	
D. J., thirty-eight year old man: alcoholic cirrhosis with jaundice, ascites and periodic encephalopathy	3/18/57 A	Grade 2	160	Transferred from another hospital on 3/17 with flapping tremor, garrulity and disorientation; gradual mild improvement in orientation was evident until 3/28 when hematemesis occurred followed by deep coma and death
		Improved 1+	150	
	3/26/57 G	Grade 1 to 2	110	
		Improved 1+	110	

\* G = 5% glucose in water.

A = L-arginine solution.

TABLE I (Continued)

CLINICAL DATA ON PATIENTS WHO SHOWED SOME IMPROVEMENT WHEN TREATED WITH L-ARGININE OR GLUCOSE

Patient and Disorder	Date and Treatment *	State of Encephalopathy before and after Treatment	Arterial NH <sub>4</sub> before and after Treatment (μg./100 ml.)	Clinical Course
W. G., forty-five year old man: alcoholic cirrhosis with jaundice and subacute osteomyelitis of the foot	3/29/57 A	Grade 3	190	Hospitalized 3/27/57, with ascites, confusion and flapping tremor; no change was noted following arginine although he seemed less lethargic on 3/30/57; after the glucose infusion his flapping tremor seemed improved and his signature was more legible; slow steady improvement continued until his discharge on 5/9/57
		No change	160	
	4/3/57 G	Grade 2	140	
		Improved 1+	80	
A. F., forty-five year old man: alcoholic cirrhosis with jaundice and ascites	5/23/57 A	Grade 3	160	Hospitalized on 5/22/57, with moderate confusion which progressed to a lethargic semistuporous state on 5/23/57; he was considerably more alert and orientated after the arginine infusion but became worse again on 5/24, with a drop in blood pressure and oliguria; several tarry stools were passed on 5/27; he remained in deep coma until 5/28 at which time he improved amazingly without specific therapy; he gradually improved thereafter and was discharged on 7/4/57
		Improved 3+	230	
	5/24/57 G	Grade 3	190	
		No change	200	
M. G., forty-eight year old man: alcoholic cirrhosis with jaundice and ascites	6/12/57 G	Grade 1	100	Lethargy and flapping tremor accompanied jaundice, ascites and edema at the time of hospitalization on 6/10/57; he seemed more alert following the glucose infusion with little change in tremor; on 6/13 he was markedly improved with no signs of encephalopathy; flapping tremor and lethargy gradually reappeared; on 6/19 his condition deteriorated in spite of the arginine infusion and on 6/20 he died in deep coma
		Improved 1+	80	
	6/19/57 A	Grade 1	160	
		Worse 2+	160	
J. H., thirty-eight year old woman: biliary cirrhosis following ten years of common duct stricture with recurring cholangitis	6/12/57 A	Grade 2	100	Evidences of encephalopathy (gross flapping tremor and confusion) appeared after the tenth attempt to relieve her problem surgically; after the arginine infusion the confusion seemed a little less; however, she became worse that night; the confusion then gradually improved and on 6/19 she manifested only gross flapping tremor which diminished markedly after the glucose infusion; all signs of encephalopathy disappeared by 6/24
		Improved 1+	90	
	6/19/57 G	Grade 1	170	
		Improved 2+	180	
F. G., fifty year old man: alcoholic cirrhosis with jaundice	7/5/57 A	Grade 3	120	Hospitalized 7/1/57 in deep coma of two to three days' duration; his condition improved slightly and on 7/5/57 he responded when asked his name; following the arginine infusion he seemed to respond more readily but was otherwise unchanged; on 7/8/57 he was noted to be much less lethargic and more responsive but on 7/9 he became stuporous again and died.
		Improved 1+	160	

TABLE I (Continued)

CLINICAL DATA ON PATIENTS WHO SHOWED SOME IMPROVEMENT WHEN TREATED WITH L-ARGININE OR GLUCOSE

Patient and Disorder	Date and Treatment*	State of Encephalopathy before and after Treatment	Arterial NH <sub>4</sub> before and after Treatment (μg./100 ml.)	Clinical Course
J. C., forty year old man: alcoholic cirrhosis with chronic ascites and mild jaundice	7/24/57 G	Grade 2	360	Encephalopathy had been noted intermittently for six months during which time he had ascites and low grade jaundice; on 7/24 he had flapping tremor, slow responses and mild disorientation; his responses and orientation seemed improved following glucose; his condition was unchanged on 7/25 and did not improve after arginine; he was discharged on 8/3/57 with evidence of continued mild encephalopathy
		Improved 1+	200	
	7/25/57 A	Grade 2	105	
		No change	230	
T. O., forty-eight year old woman: chronic congestive cirrhosis (mitral stenosis and tricuspid insufficiency)	8/7/57 A	Grade 3	240	The onset of hepatic coma (manifested by fetor hepaticus, gross flapping tremor and semistupor) was abrupt and unexplained in this patient, six months after mitral valvotomy; she entered the hospital on 8/6 in deep coma; some improvement was evident on the morning of 8/7 and there was marked lessening of her lethargy following the arginine infusion in the afternoon; although no definite change was noted immediately after the glucose infusion, there was progressive improvement from 8/8 to 8/11 when all signs of encephalopathy were gone; she was discharged 9/6/57
		Improved 3+	200	
	8/8/57 G	Grade 2	200	
		No change	190	
G. G., eighty-one year old man: alcoholic cirrhosis with ascites	8/15/57 G	Grade 2	...	Confusion and flapping tremor had been noted intermittently since June 1957, occasionally precipitated by NH <sub>4</sub> Cl and occasionally without obvious cause; he was hospitalized 8/14/57 with tremor, mild lethargy and confusion; mild improvement in orientation was noted after the arginine infusion and gradual improvement continued until discharge on 8/19/57 with minimal residual encephalopathy
		No change	...	
	8/16/57 A	Grade 2	...	
		Improved 1+	...	
R. B., forty-eight year old woman: alcoholic cirrhosis with ascites	8/21/57 G	Grade 3	120	Gradual onset of encephalopathic behavior on 8/15/57; on 8/21 disorientation, marked lethargy and flapping tremor were evident; after the glucose infusion, she seemed much more responsive and would answer some questions rationally; further significant improvement was evident on the morning of 8/22; no change was noted after arginine and on 8/23 she rapidly became worse and died
		Improved 2+	210	
	8/22/57 A	Grade 2	230	
		No change	230	

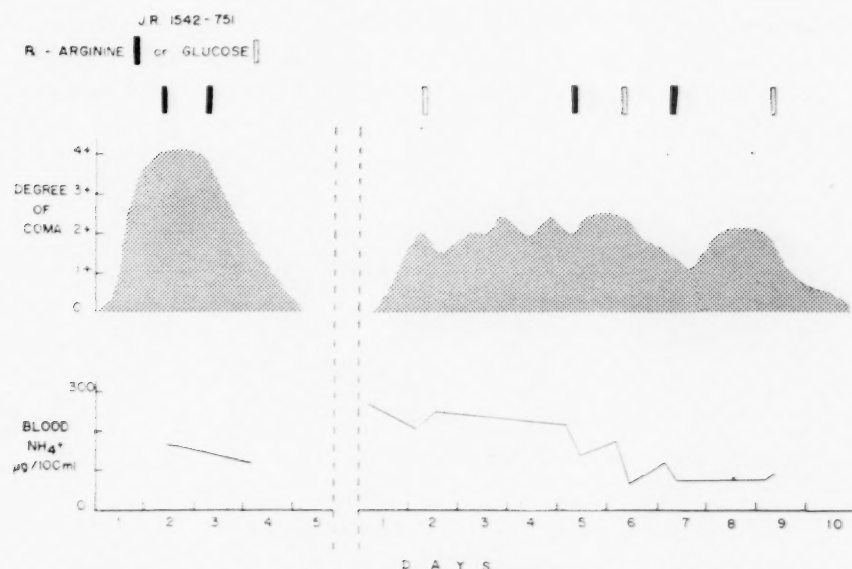


FIG. 2. Effect of L-arginine on two episodes of hepatic encephalopathy, uncontrolled vs. controlled observations.

study we attempted to minimize these variables by including only a few patients in whom encephalopathy resulted either from ammonium chloride ingestion, from gastrointestinal bleeding, or from a portacaval shunt. The majority of our patients, therefore, were considered to have encephalopathy on the basis of liver cell failure. The prognosis is poorest in this group of patients, nevertheless it is here that a therapeutic agent is most needed and must demonstrate its efficacy to be of any real value.

Our conclusions regarding the effect of arginine differ considerably from those of Najarian and Harper [7]. Varying degrees of improvement followed arginine infusion in each of their fifteen patients. There was a fall in venous  $\text{NH}_4$  in every case although it was often of small magnitude. The mean  $\text{NH}_4$  level prior to the twenty-four arginine infusions listed in their data was  $164 (\pm 10.6) \mu\text{g./100 ml.}$  and the mean value after arginine was  $125 (\pm 11.6) \mu\text{g./100 ml.}$  This is a greater fall than we noted in our patients and is statistically significant.\*

A possible reason for the difference in results lies in the type of patient chosen for study. The factor precipitating encephalopathy appeared to be hemorrhage from esophageal varices in six of their patients. Ammonium chloride had been administered to another, and three pa-

tients had had antecedent portacaval or spleno-renal shunts. As indicated previously, we believe that in patients of this sort evaluation of the effects of therapy may prove to be difficult without the use of controls.

An illustration of the advantages of controlled observations is provided in Figure 2. The patient is J. R., a fifty-two year old seaman with alcoholic cirrhosis. A portacaval shunt was performed on December 6, 1957, because of previous hematemesis from esophageal varices. Ten months after the shunt the first of several subsequent episodes of encephalopathy occurred. In the first portion of Figure 2 is seen the patient's apparently dramatic response to two infusions of L-arginine. Immediately following the second infusion he began to arouse from a deeply comatose state and was able to leave the hospital four days later. The double blind technique for arginine evaluation was not in operation at this time. On another admission with a somewhat lesser degree of encephalopathy both arginine and glucose were administered as part of the current investigation. Moderate improvement seemed to follow each of the first two infusions of glucose. After the first arginine treatment he became worse and after the second he improved minimally. Concurrently with the third infusion of glucose his encephalopathy virtually disappeared. In retrospect it seemed unlikely to us that L-arginine had anything to do with his recovery in either instance.

\* The observed difference between the means (39) is more than twice the standard error of the difference between the means (15.6).

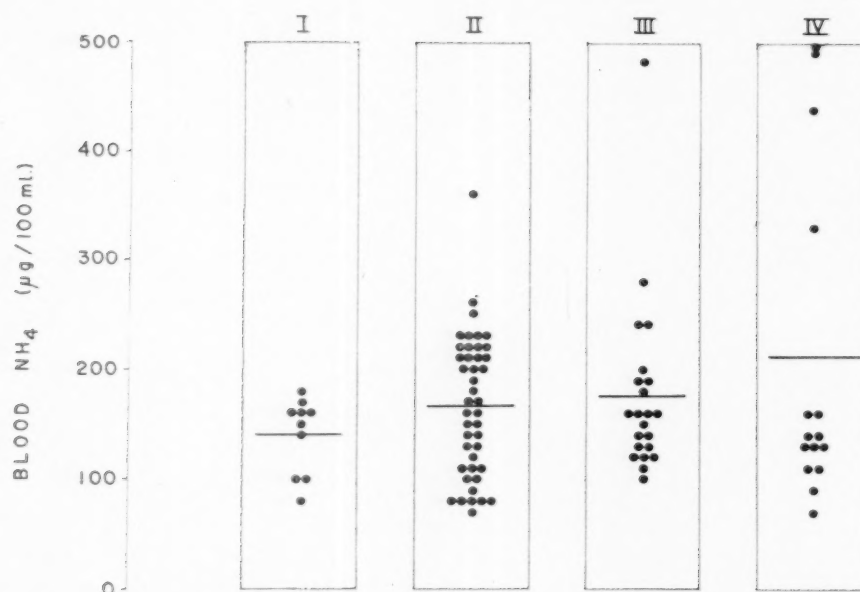


FIG. 3. Arterial  $\text{NH}_4$  levels in different grades of encephalopathy. For definition of grades 1 to 4, see text.

An additional way to evaluate the efficacy of L-arginine therapy would be to demonstrate enhancement of urea synthesis from ammonium, as was done in liver slices by Greenstein *et al.* [2]. Initially we planned to note the effects of the infusions given in the present study on blood urea levels. This plan was abandoned, however, because of our inability to evaluate the influence of renal function on the blood urea level. Renal function was often changing and impaired in our patients as it is in many patients with terminal liver disease. Metabolism of the infused arginine might contribute to urea formation and thus render non-comparable the postinfusion blood urea levels after glucose and arginine even in the absence of renal functional changes.

As a sidelight of the present study it is of interest to compare arterial  $\text{NH}_4$  levels with the degree of encephalopathy present in our patients. Previous publications have called attention to the lack of a close correlation between venous  $\text{NH}_4$  level and the severity of hepatic coma [5,13,16]. Bessman has pointed out a potential arterial-venous  $\text{NH}_4$  difference due to  $\text{NH}_4$  uptake in peripheral tissues which could provide an explanation for the poor correlation between clinical condition and venous  $\text{NH}_4$  values [14]. When we began this study, arterial rather than venous  $\text{NH}_4$  values were measured in the hope that they would show better correlation with clinical encephalopathy. Figure 3 indicates that even this correlation is poor. Although the mean

arterial  $\text{NH}_4$  level rises in each succeeding grade of encephalopathy, the individual  $\text{NH}_4$  values have little clinical significance as evidenced by the relatively low levels noted in several of the grade 4 patients. Whether this implies that some nitrogenous component other than ammonium is the cause of hepatic encephalopathy or that existing methods for the measurement of blood ammonium are inadequate we do not know.

The results of our investigation concededly do not positively exclude a beneficial effect from L-arginine therapy in hepatic encephalopathy. Too many factors remained uncontrolled to warrant such definite conclusions in the face of a contradictory report [7]. Our results with arginine are not in harmony with the experiments in animals already cited [1-4]. An obvious difference between the animal studies and our clinical experiments is the state of liver function in the subjects. It seems plausible that arginine or other amino acid substrates of the Krebs-Henseleit cycle could be rate-limiting in the process of urea formation in a liver with normal enzyme systems. Administration of these amino acids in the presence of ammonium overload then could be expected to enhance ammonium removal. In the human patient with severe liver disease, on the other hand, all evidence points away from any deficiency of substrate for the urea cycle. Elevated plasma levels of most of the amino acids (including arginine, citrulline,

glutamine and glutamic acid) have been reported in such patients [17,18]. Under these circumstances  $\text{NH}_4$  accumulation would logically be ascribed to enzymatic deficiency rather than to lack of substrate and it is not surprising that parenteral amino acid administration is of no value.

## SUMMARY

The effect of L-arginine on the clinical state and arterial blood  $\text{NH}_4$  level of patients with encephalopathy due to hepatic failure was compared with that of a placebo solution by the double blind method. Marked clinical improvement followed arginine administration in two of thirty-four instances and followed placebo administration in one of twenty-six instances. Mild or moderate improvement accompanied an additional 24 per cent of the arginine infusions and 35 per cent of the placebo infusions.

The mean arterial  $\text{NH}_4$  level was 180  $\mu\text{g.}/100$  ml. before and 160  $\mu\text{g.}/100$  ml. after administration of arginine. The difference between the means is not statistically significant.

There was some correlation, although not a close one, between the level of arterial  $\text{NH}_4$  and the severity of the encephalopathy.

The conclusion was reached that a beneficial effect from L-arginine could not be demonstrated in this study.

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# Needle Biopsy of the Liver\*

## *Comparison of Initial Clinical and Histological Diagnoses, with a Note on Postbiopsy Mortality in Patients with Metastatic Neoplasm*

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NEEDLE biopsy of the liver has been widely adopted as an accepted procedure in the differential diagnosis of liver disease. Despite its increasing use, however, needle biopsy is a procedure to be used only in selected cases of liver disease [1].

Most reported studies have been concerned with comparison of the clinical diagnosis arrived at after the performance of liver function tests with that established by biopsy. We have attempted to assess the value of the history and physical examination in patients with liver disease by comparing the initial clinical diagnosis with the histological diagnosis as established by needle biopsy.

### MATERIAL AND METHODS

To assess our experience with this procedure we have reviewed the charts of all patients who underwent needle biopsy of the liver during a seven-year period from July 1950 to July 1957. During this time 408 biopsies were performed in 341 patients, using the Vim-Silverman needle. Of the 341 patients eighty-five were females and 256 were males. The overwhelming predominance of males can, in part, be attributed to the inclusion of experience at a Veterans' Administration Hospital which is part of this Medical Center.

### RESULTS

Of the 341 patients in whom biopsies were performed, results were of positive diagnostic significance in 226, and in the remaining 115 they were either normal or revealed non-specific changes. In nine cases the specimen was of inadequate size for pathologic diagnosis. A tabulation of diagnoses is included in Table 1. It should be noted that the second most common diagnosis on histologic examination was

that of normal liver tissue. This, in part, may be explained by the fact that some patients who were admitted to the Veterans' Hospital with vague complaints, possibly related to chronic hepatitis or posthepatic cirrhosis, have undergone biopsies in an attempt to verify this diagnosis.

In 201 patients the initial diagnosis was proved correct. In twenty-six cases the biopsy revealed fatty metamorphosis when the clinical impression was that of cirrhosis [2-4]; in these instances the clinical diagnosis cannot be considered to be in gross error. However, in the remaining 114 patients (33.4 per cent) the clinical impression was subsequently changed by the biopsy.

A comparison of the erroneous initial clinical impressions and the biopsy diagnoses, with the number of patients in each group, is given in Table II. In twelve patients extrahepatic biliary obstruction was suspected clinically but not confirmed on biopsy. In an additional eight patients biopsy revealed extrahepatic obstruction which was not suspected clinically. In these cases the biopsy was of great aid in determining the need for surgery. In thirty cases metastatic carcinoma was clinically diagnosed but not found at biopsy, while in fourteen instances biopsy revealed metastatic carcinoma which was not clinically suspected. Thus in forty-four cases the prognosis was altered by finding an unsuspected malignancy, or an expected malignancy was not found. In the remaining fifty cases neither the therapy nor the prognosis was greatly altered by the biopsy, although the histologic interpretation was not the same as the clinical diagnosis.

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In eight instances the biopsy was proved to be in error. In five of these patients biopsy revealed a normal liver although the clinical impression was metastatic malignancy and at laparotomy or autopsy metastatic malignancy of the liver was present. In two patients who clinically were

not consistent with the initial clinical diagnosis, the error in diagnosis is reduced to 30.2 per cent. This figure approximates that of other studies in which the biopsy was compared with the final clinical impression after an adequate series of liver function studies had been per-

TABLE I  
TABULATION OF DIAGNOSIS AS ESTABLISHED BY  
NEEDLE BIOPSY OF THE LIVER IN 341 PATIENTS

Diagnosis	Patients	
	No.	Per cent
Cirrhosis . . . . .	77	22.6
Normal . . . . .	66	19.4
Fatty metamorphosis . . . . .	54	15.8
Non-specific changes . . . . .	36	10.6
Metastatic carcinoma . . . . .	33	9.7
Hepatitis . . . . .	26	7.6
Extrahepatic biliary obstruction . . . . .	11	3.2
Inadequate specimen . . . . .	9	2.6
Biliary cirrhosis . . . . .	7	2.1
Chlorpromazine toxicity . . . . .	5	1.5
Hemochromatosis . . . . .	4	1.2
Granuloma . . . . .	3	0.9
Diabetes . . . . .	2	0.6
Passive hyperemia . . . . .	2	0.6
No hepatic tissue . . . . .	2	0.6
Lymphoma or leukemia . . . . .	2	0.6
Abscess . . . . .	1	0.3
Hemangioma . . . . .	1	0.3

diagnosed as having obstructive jaundice liver biopsy specimens were normal. At laparotomy one of these patients had a stricture of the common bile duct while the other had lymphosarcoma with compression of the common bile duct. In the eighth case the clinical diagnosis was portal cirrhosis but biopsy revealed non-specific changes. Subsequent biopsy at laparotomy confirmed the clinical diagnosis of portal cirrhosis.

In three additional cases biopsy probably yielded a false negative result. All three patients were suspected of having metastatic malignancy involving the liver, however, needle biopsy revealed a normal liver in each. In two of these patients malignant neoplastic cells were recovered from paracentesis fluid; the sputum of the third patient was positive for neoplastic cells.

If these eleven false negatives are subtracted from the 114 patients in whom the biopsy was

TABLE II  
INITIAL CLINICAL DIAGNOSES WHICH WERE DETERMINED  
TO BE WRONG BY NEEDLE BIOPSY OF THE LIVER

Prebiopsy Diagnosis	Biopsy Diagnosis	No. of Patients
Cirrhosis . . . . .	Extrahepatic obstruction	5
Cirrhosis . . . . .	Hepatitis	1
Cirrhosis . . . . .	Metastatic carcinoma	6
Cirrhosis . . . . .	Normal	26
Cirrhosis . . . . .	Passive congestion	1
Cirrhosis . . . . .	Fatty metamorphosis	26
Hepatitis . . . . .	Normal	12
Hepatitis . . . . .	Extrahepatic obstruction	2
Hepatitis . . . . .	Abscess	1
Hepatitis . . . . .	Cirrhosis	7
Hepatitis . . . . .	Fatty metamorphosis	3
Hepatitis . . . . .	Chlorpromazine toxicity	1
Extrahepatic obstruction . . . . .	Cirrhosis	2
Extrahepatic obstruction . . . . .	Metastatic carcinoma	3
Extrahepatic obstruction . . . . .	Normal	4
Extrahepatic obstruction . . . . .	Fatty metamorphosis	3
Metastatic carcinoma . . . . .	Cirrhosis	8
Metastatic carcinoma . . . . .	Fatty metamorphosis	6
Metastatic carcinoma . . . . .	Normal	12
Metastatic carcinoma . . . . .	Granuloma	1
Metastatic carcinoma . . . . .	Hemochromatosis	1
Metastatic carcinoma . . . . .	Hemangioma	1
Metastatic carcinoma . . . . .	Extrahepatic obstruction	1
Passive congestion . . . . .	Cirrhosis	1
Lymphoma . . . . .	Metastatic carcinoma	1
Lymphoma . . . . .	Cirrhosis	3
Lymphoma . . . . .	Hepatitis	2

formed [5-9]. Schiff states that the clinical examination of patients with jaundice should lead to the correct diagnosis in 60 to 80 per cent of the cases [10].

Liver biopsies were requested and performed most frequently in those cases in which there was doubt as to the accuracy of the clinical diagnosis. Biopsies performed in patients of this type would reveal a greater error in the clinical diagnosis than if all patients with liver disease underwent biopsy. Therefore most studies of a series of biopsies, including this one, tend to show a greater error in clinical diagnosis than exists.

*Mortality Following Needle Biopsy of the Liver.* In an extensive review of experience with needle biopsies Zamcheck and Klausenstock [11] noted thirty-nine deaths occurring in 20,000 biopsies. Our experience, however, has not been so fortunate and suggests that mortality will vary with the type of disease under study.

Prothrombin determinations were performed

in all our patients and no patient underwent biopsy if the prothrombin activity was less than 60 per cent of normal. No biopsies were performed in the presence of a known hemorrhagic disorder or severe anemia. In spite of these precautions death occurred in association with hemorrhage in five patients, a mortality of 1.5 per cent. Four of these patients had metastatic carcinoma of the liver which was found in biopsy specimens. These patients were part of a total of thirty-three patients with metastatic carcinoma who underwent biopsy. Thus the mortality rate in the presence of metastatic carcinoma was 12 per cent. The biopsy in all five of these patients was performed by a physician experienced in the procedure. The salient features of these cases are described in the following paragraphs.

CASE I. R. C., a thirty-three year old white housewife, gravida vi, para vi, was admitted to the Syracuse Memorial Hospital on July 16, 1951, with a chief complaint of vaginal bleeding. Six weeks previously, at another hospital, she had undergone hysterectomy and left salpingo-oophorectomy for what was reported to be myoma uteri and ovarian cyst. Routine chest film at that time revealed a mass in the left side of the chest. In the ensuing six weeks, the patient lost twenty-five pounds and required several blood transfusions.

Physical examination revealed a thin, chronically ill white woman with a temperature of 100.5°F., pulse 104, respirations 22 and blood pressure 120/50 mm. Hg. Dullness, diminished breath sounds and diminished tactile and vocal fremitus were present at the basilar portion of the left lung. The liver was enlarged to below the iliac crest and was tender; no nodules were felt. The spleen was palpable 3 to 4 cm. below the left costal margin. The hemoglobin was 9 gm. per cent, hematocrit 26 volumes per cent, white blood cell count 8,200/cu. mm., with a normal differential count. The urine was acid, specific gravity 1.022, albumin 2 plus, sugar 1 plus, and acetone negative. There were 2 to 4 red and white blood cells per high power field. The serum total protein was 4.8 gm./100 ml., albumin 3.1 gm. and globulin 1.7 gm., cephalin flocculation test 1 plus, serum bilirubin within normal limits, Coombs' test negative, and prothrombin activity 80-90 per cent of normal. X-ray examination of the chest showed a well circumscribed mass, 5 cm. in size, lying posteriorly in the left thorax.

On July 20, 1951 a needle biopsy of the liver was obtained through the tenth intercostal space in the anterior axillary line, a previous attempt through the ninth space having failed. Bleeding through the needle was noted on both occasions. During the

procedure the patient complained of pain in the right shoulder. The patient's course was uneventful for forty-eight hours, followed by the sudden onset of shock with a pulse of 168, respirations 60, and blood pressure 80/0 mm. Hg. The hemoglobin at this time was 6 gm./100 ml. She was given plasma, blood, neo-synephrine® and vitamin K. During the next four hours she gradually improved, the blood pressure rising to 120/54 mm. Hg with a pulse rate of 100. There was slight tenderness over the lower abdominal quadrants but no spasm. She was complaining of pain in the right shoulder. Fifty-four hours after biopsy she suddenly died. Permission for postmortem examination was refused. The liver biopsy specimen revealed choriocarcinoma.

This patient probably experienced a significant hemorrhage forty-eight hours after the liver biopsy, as evidenced by the development of shock and fall in hemoglobin. This hemorrhage may have been unrelated to the biopsy procedure, or if related was slow in development. Her sudden death at a time when the vital signs were stable is difficult to explain. Unfortunately, an autopsy was not performed. The biopsy probably played a role in causing death but this was not conclusively demonstrated.

CASE II. F. B., a fifty-six year old man, was admitted on September 28, 1952, to the Syracuse University Hospital with high fever, disorientation and a productive cough. Six weeks prior to admission, chills and fever associated with a non-productive cough developed which became productive two weeks prior to admission. A 30-pound weight loss had occurred during these six weeks.

Physical examination revealed a poorly nourished, well developed, white man who was lethargic and confused. The temperature was 104°F., pulse, 120, respirations 40 and blood pressure 120/80 mm. Hg. There were bronchial breath sounds and crepitant rales throughout both lung fields. The liver was tender and palpable 6 cm. below the costal margin. The spleen was not palpable. The hemoglobin was 12.2 gm. per cent, hematocrit 38 volumes per cent, white blood cell count 3,700/cu. mm. with a normal differential count. The urinalysis was normal except for 1-plus albuminuria. The blood non-protein nitrogen was 47 mg./100 ml. fasting blood sugar 84 mg./100 ml., serum bilirubin 1.4 mg./100 ml. (direct 0.5 mg.), total protein 5.1 gm./100 ml. with albumin 2.6 gm. and globulin 2.5 gm., cephalin flocculation test trace, bromsulphalein retention 17 per cent in 45 minutes, prothrombin activity 90 per cent of normal.

On October 18 a liver biopsy was performed through the ninth intercostal space in the anterior axillary line without incident. This specimen revealed multiple granulomas with necrotic centers, and epithelioid and rare giant cell reaction. During the next three weeks the patient had a progressive downhill course. The prothrombin activity on November

10 was 80 per cent. On November 11, while the patient was semicomatose, a second liver biopsy was performed through the ninth intercostal space in the anterior axillary line. The patient died twenty-four hours later without a significant change in blood pressure or pulse. The second liver biopsy revealed granulomas which were tuberculoid in type; no histoplasma were seen using the MacManus technique. Autopsy revealed approximately 1,000 ml. of blood and blood clots in the peritoneal cavity. The liver weighed 2,590 gm. On the right lateral surface of the liver there were three puncture wounds produced by the needle biopsy. Two were small while one was a 0.6 cm. tear in the liver substance; this tear was filled with recently clotted blood. A 0.2 cm. perforation of the stomach was noted and thought to be agonal. In addition, acute miliary tuberculosis was present.

Biopsy of the liver in this moribund patient resulted in a tear of the capsule with subsequent hemorrhage. This probably hastened his death, which appeared to be imminent.

CASE III. A. S., a seventy-five year old man, was admitted to the Crouse-Irving Hospital on September 29, 1956, with chief complaints of cough of four to six weeks' duration, fatigue, weakness, anorexia, and a 10-pound weight loss in the past four weeks. Two weeks prior to admission an x-ray of the chest had disclosed a lesion in the left mid-lung field which was thought to be either neoplastic or inflammatory.

Physical examination revealed a well developed, thin, chronically ill white man who was cooperative and oriented. The pulse was 80, respirations 20, temperature 100°F., and blood pressure 180/90 mm. Hg. A hard node, 1 cm. in diameter, was palpable in the left supraclavicular area. There were rales in the left mid-lung field, without dullness or change in the quality of the breath sounds. The liver was tender and palpable 6 cm. below the costal margin. The hemoglobin was 13.5 gm. per cent, hematocrit 43 volumes per cent, white blood cell count 42,200/cu. mm. with 88 per cent polymorphonuclear leukocytes and 12 per cent lymphocytes. Urinalysis showed a specific gravity of 1.013, albumin 3 plus, sugar negative. Microscopic examination showed 5 to 10 red blood cells per high power field. The blood non-protein nitrogen was 35 mg./100 ml., fasting blood sugar 115 mg./100 ml., serum total protein 7.8 gm./100 ml., albumin 4.8 gm. and globulin 3.0 gm., bromsulphalein retention 8 per cent in forty-five minutes, alkaline phosphatase 4.4 Bodansky units, and prothrombin activity 65 per cent of normal.

After a biopsy of the lymph nodes which revealed chronic lymphadenitis a needle biopsy of the liver was performed through the tenth intercostal space in the anterior axillary line on October 9. Within thirty to sixty minutes following the biopsy the patient began to complain of severe low back pain, the blood

pressure fell to 88/50 mm. Hg, and the pulse rose to 110. The abdomen remained soft. The hematocrit dropped to 33. A peritoneal aspiration failed to reveal free blood. During the ensuing evening the patient was transfused with three units of blood and the blood pressure gradually stabilized at approximately 170/100 mm. Hg. The hematocrit, however, remained at approximately 33 volumes per cent. Thirty-six hours later the back pain, which had subsided, recurred and the hematocrit was 16 volumes per cent. Peritoneal aspiration revealed free blood. Laparotomy was performed at which time 1 L. of old clotted and dark red blood was removed from the peritoneal cavity. A tear about 3 cm. in length, from which a small amount of dark red blood was oozing, was found on the lateral surface of the liver. Oxycel® was applied and the laceration was sutured with difficulty due to marked friability of the liver. The liver was noted to be studded with small metastatic nodules. Following surgery the patient remained semicomatose. The following day the blood pressure fell to 70/30 mm. Hg and the temperature and pulse rose to 106°F. and 144 respectively. The hematocrit at this time was 30 volumes per cent. The patient died forty-eight hours after biopsy and twenty-four hours after exploration. Permission for postmortem examination was refused. The needle biopsy specimen revealed nests of spindle and round metastatic carcinoma cells suggesting an oat cell carcinoma of the lung as the primary site.

At the time of introduction of the biopsy needle it was noted that the patient took a deep breath. It is probable that this accounted for the large tear in the liver capsule with subsequent hemorrhage. The fact that the liver was friable at laparotomy suggests that this may have increased the likelihood of bleeding. Whether or not the friability was due to the presence of the tumor cannot be definitely stated. It is quite likely that the patient had recurrent hemorrhage following laparotomy in view of the recurrent shock which preceded death.

CASE IV. C. T., a seventy-nine year old white man, was admitted to the Syracuse University Hospital on January 5, 1957, with the chief complaint of backache of three months' duration. Two months prior to admission the patient noted the onset of diffuse abdominal pains and enlargement of the abdomen. He had noted a 15-pound weight loss in the past four to six months.

Physical examination revealed a well developed, thin, chronically ill, elderly white man. The temperature was 98°F., pulse 84, respirations 20 and blood pressure 140/90 mm. Hg. The abdomen was distended with ascites. The liver was hard and palpable 5 cm. below the costal margin. There was 3-plus pitting edema of the legs. The hemoglobin was 14.7 gm. per cent, hematocrit 45 volumes per cent, white blood cell count 6,400/cu. mm. with 59 per cent polymor-

phonuclear leukocytes and 41 per cent lymphocytes. The urine was cloudy, specific gravity 1.018 with a faint trace of albumin and a trace of sugar. Microscopic examination revealed 4 to 8 red blood cells and 15–25 white blood cells per high power field. The blood non-protein nitrogen was 35 mg./100 ml., fasting blood sugar 118 mg./100 ml., serum total protein 5.8 gm./100 ml. with 3.3 gm. of albumin and 2.5 gm. of globulin, cephalin flocculation test 4 plus, alkaline phosphatase 11.8 Bodansky units, and prothrombin activity 75 per cent of normal.

On January 14 a needle biopsy of the liver was performed through an epigastric approach. Approximately one hour later the patient was in shock, with no blood pressure or pulse obtainable. The hematocrit at this time was 27 volumes per cent. Peritoneal aspiration revealed bloody ascitic fluid. The patient was treated with intravenous fluids, norepinephrine and blood replacement. Laparotomy was performed at which time 3,500 ml. of bloody ascitic fluid was aspirated. A blood clot was found over the dome of the liver. Removal of the clot revealed three puncture marks in a metastatic nodule, two of which were oozing a small amount of blood. Hemostasis was effected by suture and gelfoam over the puncture holes. Postoperatively the patient had a gradual downhill course and died on the fifth day after biopsy. The needle biopsy specimen revealed metastatic adenocarcinoma, consistent with carcinoma of the pancreas. Postmortem examination revealed 2,000 cc. of pink fluid in the peritoneal cavity. The liver weighed 2,000 gm. Removal of the gelfoam from the right lobe of the liver revealed a very small amount of clotted blood over a 0.2 cm. puncture wound. Almost the entire right lobe of the liver was replaced by grayish tumor which showed areas of necrosis and hemorrhage. There were discrete nodules of tumor in the left lobe. The body and the tail of the pancreas were replaced by firm, grayish scirrhous tumor.

Hemorrhage occurred in this case without laceration of the capsule, but the biopsy puncture had entered a nodule on the surface of the liver.

**CASE V.** A. P., a sixty-three year old white woman, was admitted to the Crouse-Irving Hospital on January 29, 1957, with the chief complaints of weakness, anorexia, and vomiting of one month's duration.

Physical examination revealed an obese white woman in no acute distress. The temperature was 99°F., pulse 80, respirations 20, and blood pressure 110/60 mm. Hg. Scleral icterus was present. There was dullness with diminished breath sounds at the right lung base. The liver was hard, tender, palpable 5 cm. below the costal margin and extended across the epigastrium. The spleen edge was just palpable. Ascites, as evidenced by shifting dullness, were present. There was paralysis of the right leg and foot. Positive Babinski and Hoffmann signs were elicited on the right. The hemoglobin was 10 gm. per cent,

hematocrit 32 volumes per cent, white blood cells 9,800/cu. mm. with 75 per cent polymorphonuclear leukocytes, 23 per cent lymphocytes and 2 per cent eosinophils. The urinalysis was within normal limits except for a trace of albumin. The blood non-protein nitrogen was 24 mg./100 ml., serum bilirubin 0.57 mg./100 ml., serum total protein 6.0 gm./100 ml., cephalin flocculation test 2 plus, alkaline phosphatase 26.9 Bodansky units, and prothrombin activity 90 per cent of normal.

The patient was transfused with 3 units of blood, with a rise in hematocrit to 42 volumes per cent. On February 13 a needle biopsy was performed through the tenth intercostal space in the anterior axillary line. Approximately forty-five minutes following biopsy the patient went into shock with a pulse of 150 and a blood pressure of 60/40 mm. Hg. Norepinephrine infusion was started, with an increase in blood pressure to 90/60 mm. Hg. The hematocrit at this time was 37 volumes per cent and peritoneal aspiration yielded dark blood. The patient was transfused with 5 units of blood. Pulmonary edema developed which was treated with a digitalis preparation, rotating tourniquets and demerol.<sup>®</sup> The patient died approximately twenty-four hours after biopsy. The last hematocrit prior to death was 47 volumes per cent. Liver biopsy showed anaplastic carcinoma with much necrosis and a pattern suggestive of pulmonary carcinoma as the primary site. Postmortem examination revealed approximately 800 ml. of blood in the peritoneal cavity. A massive clot measuring 6 cm. in its widest diameter was present over the inferior margin of the liver, particularly on the right side. Upon removal of the clot the site of the biopsy was seen to exude blood freely. The biopsy site measured 0.1 cm. in diameter; no evidence of tear was present and the biopsy did not go through a nodule of tumor at this point. The liver weighed 5,290 gm. Examination of the external surface revealed multiple, umbilicated nodules and section of the liver revealed diffuse replacement of the parenchyma by tumor. The needle biopsy tract was traced through the liver and at its distal end it impinged upon a small nodule of tumor. The remainder of the examination revealed a carcinoma of the right lower lobe bronchus with metastases to bone, nodes and duodenum. In addition, both adrenals were replaced by neoplastic tissue.

Although hemorrhage followed needle biopsy it probably was not the cause of death since blood replacement was more than adequate. The extensive replacement of both adrenals with tumor suggests that the hemorrhage may have precipitated adrenal insufficiency. The cause of the hemorrhage is difficult to explain as no laceration of the liver occurred.

#### COMMENTS

In four of these five fatal cases laparotomy or autopsy or both confirmed the role of the biopsy

procedure in the clinical course. In R. C., Case I, it is probable that hemorrhage following biopsy contributed to her death. It is noteworthy that the only symptom referable to the intraperitoneal hemorrhage in these patients was the development of shock. Abdominal pain was not noted but one patient did experience low back pain while another noted pain in the right shoulder due to pleural irritation.

The association of fatality following needle biopsy with metastatic disease in the liver thus would seem to deserve more attention than it has received. Although the occurrence of hemorrhage has been said to be increased [12] in such patients, we have been unable to confirm this in a review of the literature. In a review of thirty-nine reported deaths following needle biopsy Zamcheck and Klausenstock [17] noted that hemorrhage was implicated in twenty-nine. In only five of these patients was metastatic carcinoma present and in three the prothrombin concentration was either not determined or was below what is usually considered to be a safe level.

Our experience suggests that percutaneous needle biopsy is potentially dangerous in suspected malignant disease of the liver. Surgical biopsy under local anesthesia in such cases would have the advantage of adequate visualization of the liver and thereby reduce the number of false negative results as well as decrease the incidence of uncontrolled hemorrhage.

#### SUMMARY

1. The admission clinical diagnosis has been compared with the histologic diagnosis in 341 patients undergoing needle biopsy of the liver.
2. The initial clinical diagnosis was in error in 30.2 per cent of the cases.
3. The histologic diagnosis as established by needle biopsy was proved by laparotomy or autopsy to be in error in eight cases. Errors in diagnosis probably occurred in three additional

cases, as demonstrated by cytologic study of ascitic fluid and sputum.

4. Five deaths occurred following biopsy. Intraperitoneal hemorrhage was proved in four of these patients. Four deaths occurred in patients with metastatic malignancy, for a biopsy mortality of 12 per cent under these circumstances.

5. Needle biopsy of the liver in the presence of suspected malignant disease is hazardous and surgical biopsy under local anesthesia may be a preferable procedure in this situation.

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# Islet Cell Tumor and a Syndrome of Refractory Watery Diarrhea and Hypokalemia\*

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THE object of this paper is to draw attention to a syndrome of diarrhea, hypokalemia and death from renal failure in association with islet cell tumor. Refractory peptic ulceration in association with islet cell tumors has been given prominence recently by Zollinger and Ellison [7,2]. With the exception of a case reported by Priest and Alexander [3], the early occurrence of diarrhea in many of the cases reported on has not been clearly recognized and discussed.

## CASE REPORTS

CASE 1. A sixty-seven year old Negro man was admitted to Duke Hospital on March 27, 1957. He had been well until ten months prior to admission when diarrhea developed with passage of two or three watery stools daily. He also had weekly attacks of cramping abdominal pain lasting approximately thirty minutes. The diarrhea gradually became more severe in the three months before admission and he lost 34 pounds in weight during that period. At the time of admission he had four or five liquid stools daily with occasional fecal incontinence. His mother, father, brother and sister all died before the age of forty of unknown causes.

He appeared chronically ill and wasted. The physical examination was otherwise within normal limits except for 1-plus pitting pretibial edema and a large indirect right inguinal hernia which was easily reducible.

Laboratory data disclosed a hemoglobin of 10.2 gm. per cent, hematocrit of 30.2 per cent, and white blood cell count of 5,900 per cu. mm. with a normal differential count. The urine had a specific gravity of 1.008 and contained a faint trace of protein but was otherwise normal. Three stool examinations showed no fat, ova, parasites or blood. Blood chemical findings included a fasting blood sugar of 85 mg. per cent, sodium 130 mEq./L., potassium 2.6 mEq./L., CO<sub>2</sub>

combining power 21.7 mEq./L., calcium 9.0 mg. per cent, phosphorus 2.6 mg. per cent, alkaline phosphatase 1.5 Bodansky units/100 cc., total protein 6.9 gm. per cent with 3.4 gm. per cent albumin and 3.5 gm. per cent globulin, and non-protein nitrogen 40 mg. per cent. The total two-hour urinary excretion of phenolsulfonphthalein was 50 per cent. An electrocardiogram showed sinus bradycardia with a rate of 50, P-R interval of 0.24 seconds, and small U waves suggestive of hypokalemia. A tuberculin skin test was negative in a dilution of 1:1000. X-ray of the chest showed old calcific scarring in the right mid-lung field. Roentgenograms of the gastrointestinal tract showed no abnormalities.

No cause for the diarrhea was found but it subsided somewhat with only two or three stools daily. A right inguinal herniorrhaphy was carried out at the patient's request on April 8, 1957. Postoperatively there was an exacerbation of the watery diarrhea to four or five stools daily. On the sixth postoperative day he became less responsive and decreased his dietary intake. He continued to deteriorate, becoming severely dehydrated and confused, and died on the eighth postoperative day. Blood drawn one hour prior to death revealed a non-protein nitrogen of 175 mg. per cent, sodium 143 mEq./L., potassium 2.4 mEq./L., chloride 114 mEq./L. and a CO<sub>2</sub> combining power of 10.7 mEq./L. An electrocardiogram showed marked U waves and ST segment changes compatible with hypopotassemia.

The autopsy was commenced seven hours after death. No ulceration of the gastrointestinal tract was discovered. A firm 4 by 4 by 3 cm. mass was found in the body of the pancreas. (Fig. 1.) It was pale and grayish white on external examination while its cut surface was soft and yellowish white with a few areas of a fleshy pink color scattered through it. No pituitary, adrenal, thyroid or parathyroid adenomas were seen on external examination. The kidneys were normal on gross examination. The renal tubular cells showed large clear vacuoles distending the cells and pressing

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FIG. 1. This shows the tumor mass in the body of the pancreas.

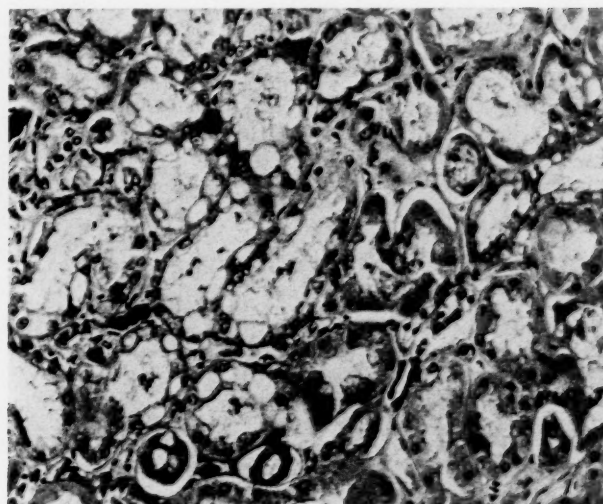


FIG. 2. The renal tubular cells contain large vacuoles.

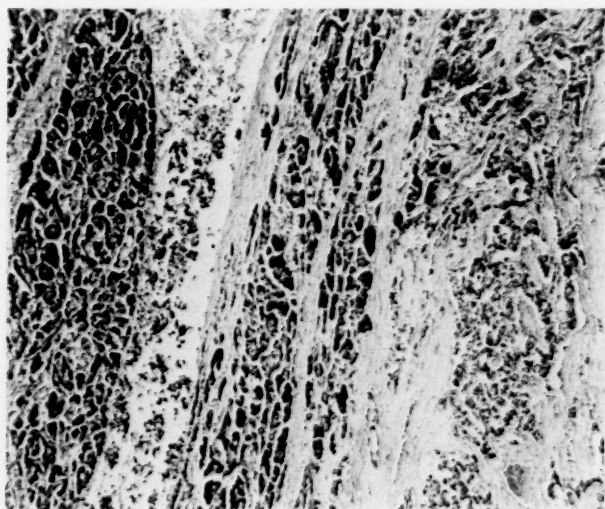


FIG. 3. The normal pancreas is seen in the left part of the picture and the tumor in the right section. Hematoxylin and eosin stain.

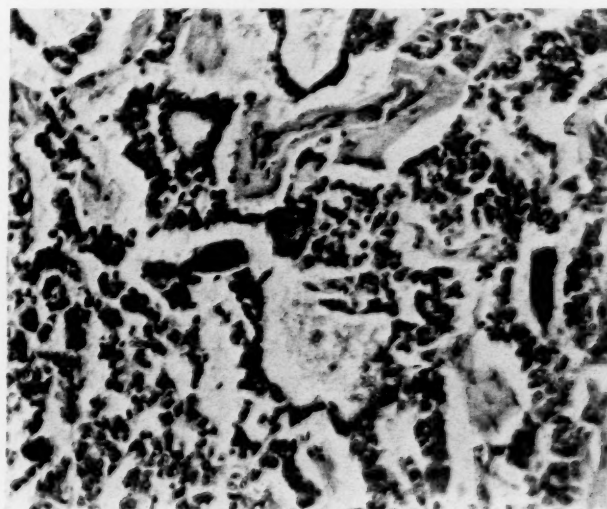


FIG. 4. A higher power view of the tumor shows the characteristic appearance of an islet cell adenoma. Hematoxylin and eosin stain.

the nuclei towards the basal portion. (Fig. 2.) These vacuoles showed no fat or glycogen on appropriate staining. The tumor of the pancreas was a well encapsulated adenoma made up of islet cells arranged in columns two or three cells thick and separated by thin-walled blood vessels showing a tendency to form gland-like acini. (Figs. 3 and 4.) The rest of the pancreatic tissue appeared normal, and no other tumors were found on exhaustive search of the organ. With the Gomori chrome-alum-haematoxylin-phloxine stain the tumor cells had a pinkish purple cytoplasm and no granules were noted except in one or two cells where eosinophilic granules of varying size were seen. The cytoplasm of the tumor cells appeared purple with the Mallory-Heidenhain stain. A small chromophobe adenoma measuring 2 by 1 mm. was found in the adenohypophysis.

SEPTEMBER, 1958

CASE II. A nineteen year old white man was admitted to Duke Hospital on July 15, 1957, with refractory diarrhea for three years. He had been admitted fourteen times since June, 1955, to the North Carolina Baptist Hospital for the same problem.

The diarrhea was characterized initially by the passage of three to four large watery stools daily. Extensive analyses of blood, urine and stools were normal and no cause for the diarrhea was found. He responded at first to treatment with a bland diet, antacids and antibiotics. Following this he had an average of about one admission to the hospital every six weeks because of recurrent symptoms of diarrhea and occasional vomiting. Although he was severely dehydrated on several occasions, with severe azotemia and hemoconcentration, no electrolyte derangements were observed until November 1955, when marked

hypercalcemia, hypophosphatemia and hypokalemia developed. (Table 1.) As hyperparathyroidism was suspected, surgical exploration of the neck was carried out. Normal parathyroids were identified, and no adenomas were present. He continued to have recurrent diarrhea, hypokalemia and dehydration with

TABLE I  
BLOOD CHEMICAL DATA IN CASE II

Data	Date				
	11/55	7/56	9/56	6/57	9/14/57
Potassium (mEq./L.)	2.1	1.8	2.3	2.8	.....
Sodium (mEq./L.)	142	.....	136	136	.....
Chloride (mEq./L.)	93	.....	.....	107	.....
CO <sub>2</sub> combining power (mEq./L.)	23.7	.....	.....	10	.....
Calcium (mg. %)	13.9	12.7	12.6	.....	12
Phosphorus (mg. %)	1.7	2.8	2.7	.....	1.7
Urea nitrogen (mg. %)	39	.....	.....	61	148

prompt improvement each time after hydration and electrolyte replacement. Electrocardiograms showed changes suggestive of hypokalemia. The specific gravity of the urine remained fixed below 1.010 even when dehydration was present. In May 1955, frank tetany and edema appeared in association with hypercalcemia and hypopotassemia. Two twenty-four urine calcium excretions were determined in June 1956, to be 40 and 82 mg. The dietary intake of calcium was not measured but a serum calcium at this time was 12.8 mg. per cent. The diarrhea had subsided by the time of admission to Duke Hospital in July 1957, when his only complaint was the passage of two to three watery stools per day.

On physical examination he appeared to be chronically ill, with decreased skin turgor and muscle tone. The blood pressure was 105/55 mm. Hg, respiratory rate 16 per minute. The remainder of the physical examination was normal.

Laboratory data included a hemoglobin of 10.8 gm. per cent, hematocrit 26.5 per cent, and a white blood cell count of 6,200 per cu. mm. with a normal differential count. The urine had a pH of 5.5 and a specific gravity of 1.008 but was otherwise not remarkable. A radioactive fat absorption study using oral I<sup>131</sup> triolein showed fat absorption to be normal. No occult blood or fat was found in the stools. Three fasting blood sugars were normal and an oral glucose tolerance test showed blood sugars as follows: fasting, 88 mg. per cent; thirty minutes, 106 mg. per cent; sixty minutes, 118 mg. per cent; 120 minutes, 106 mg. per cent; and 180 minutes, 71 mg. per cent. The serum calcium levels were 7.6, 8.8, 9.2 and 9.3 mg. per cent with concomitant phosphorus levels of 4.3, 4.6,

4.3 and 4.4 mg. per cent. The alkaline phosphatase was 1.5 Bodansky units, cholesterol 227 mg. per cent, total proteins 5.6 gm. per cent with normal albumin and globulin levels, non-protein nitrogen 25 mg. per cent, sodium 143 mEq./L., potassium 3.9, 3.7, 4.1, 4.3, 4.1 and 3.0 mEq./L., and serum amylase 124 units per hundred cc. Phenolsulfonphthalein excretion was 13 per cent in fifteen minutes and 55 per cent in two hours. The electrocardiogram was normal. During one twenty-four hour period 140 mg. of calcium and 170 mg. of phosphorus were excreted in the urine. X-ray examinations of the gastrointestinal tract, chest, skull and long bones were normal. A small renal calculus was seen in the area of the left renal pelvis on x-ray examination.

Mild diarrhea, for which no cause could be found, continued. It was considered that all of his previous electrolyte alterations had been due to diarrhea. A psychiatric consultant thought that the diarrhea might have been related etiologically to emotional problems and he was treated with psychotherapy as an outpatient through August 1957, with seeming improvement in the diarrhea. In September 1957, notification was received from the family that he had been readmitted to the North Carolina Baptist Hospital with an exacerbation of diarrhea and had died there. A summary of that admission was obtained and is summarized below.

He was readmitted to the North Carolina Baptist Hospital for the fifteenth and last time on September 8, 1957, and died eight days later. He had stopped taking his potassium chloride tablets and had a recurrence of diarrhea, nausea, vomiting and extreme weakness. The physical examination revealed him to be severely dehydrated. The blood pressure was 105/90 mm. Hg, pulse rate 66 per minute, respiratory rate 18 per minute, and temperature normal. Blood urea nitrogen was 49 mg. per cent, total serum protein 8.6 gm. per cent with a normal albumin and globulin, calcium 8.6 mg. per cent, phosphorus 2.5 mg. per cent, sodium 129 mEq./L., chloride 107 mEq./L., alkaline phosphatase 9 Bodansky units per 100 cc., and potassium 1.7 mEq./L. An electrocardiogram showed changes of hypokalemia. He was given intravenous fluids and a total of 240 mEq. of potassium daily. The diarrhea continued and progressed as an outpouring of watery stools and he gradually became semicomatose, went into shock and died on September 16, 1957. An electrocardiogram taken just before death showed ventricular fibrillation. Blood chemical findings two days before death showed a blood urea nitrogen of 148 mg. per cent, calcium 12 mg. per cent, and a phosphorus of 1.7 mg. per cent.

The autopsy was carried out two and a half hours after death at the North Carolina Baptist Hospital by Dr. Fowler to whom we are indebted for permission to quote his findings. A 2 by 4 cm. mass was found in the body of the pancreas. Microscopically, it was an islet cell adenoma, but no beta cells were present. Minimal

parathyroid hyperplasia was noted in one gland but all of the other parathyroids were normal. The kidneys showed no abnormality grossly but microscopic examination revealed large vacuoles in the convoluted tubules which did not stain for fat or glycogen. Small areas of myocardial fibrosis were seen and there was an occasional cluster of necrotic fibers. No thyroid adenomas were found. The head was not examined.

#### REVIEW OF REPORTS OF SIMILAR CASES

The association of diarrhea with non-insulin-secreting islet cell tumors is more common than has been suspected. Four cases closely similar to the ones described have been reported [1,3-5]. In all of these cases profuse diarrhea was an early symptom. In most of the cases the predominating tumor cell was of the alpha type; in no case were beta cells seen. In three other cases of islet cell tumors described previously [6-8] most attention in the reports was directed to the occurrence of recurrent peptic ulceration of the stomach, duodenum and upper jejunum although a clear history of prolonged diarrhea was present to which little or no significance was attached in the discussion. The seven cases are reviewed here to emphasize their similarity to Cases I and II of this report.

CASE III. Brown [4] described a seventy-four year old woman with diarrhea, abdominal pain, and a 14-pound weight loss. X-rays of the gastrointestinal tract revealed only a dilated duodenal bulb. At exploratory laparotomy, a 7 by 5 cm. islet cell adenoma weighing 78 gm. was found in the body of the pancreas which was said to be composed of alpha cells. The clinical symptoms were attributed to duodenal obstruction and no significance was attached to the possible secretory activity of the tumor cells. Recovery was complete, with disappearance of the diarrhea and pain.

CASE IV. Zollinger and Ellison [7] in their report of cases of severe peptic ulceration in association with islet cell adenomas include the case of a thirty-six year old woman who had had watery diarrhea for eight years with three to ten liquid stools daily. Five years after the onset of diarrhea she had first noted burning abdominal pain relieved by food and at laparotomy a jejunal ulcer had been resected. She had had several recurrences of pain over the next two years requiring further surgical procedures and ran a progressively deteriorating course with weakness, weight loss and death eight years after the onset of diarrhea. No mention was made of the presence or absence of diarrhea during the terminal illness and no potassium studies were recorded. At autopsy a 1 by 1 cm. islet cell tumor was found in the body of the pancreas.

The cell type could not be definitely established, although the cells were larger than beta cells and contained no granules. The cytoplasm of the tumor cells showed a greenish tinge on staining. There were several similar but smaller tumor nodules found in the pancreas.

CASE V. Moldawer et al. [5] reported a fifty-seven year old woman with a four year history of diarrhea, anorexia, and a 55-pound weight loss. The serum calcium was 9.5 mg. per cent and phosphorus 1.5 mg. per cent, but no potassium studies were obtained. The patient ran a downhill course culminating in skeletal muscle paralysis and death. A 7 by 7 cm. islet cell adenoma of the pancreas was found at autopsy and was said to be made up entirely of alpha cells despite the absence of granulations. No insulin could be demonstrated in the tumor by an assay carried out at the Banting and Best Institute. There was also a 1 by 1 mm. parathyroid adenoma as well as a small thyroid adenoma. Vacuolar changes were seen in the renal tubules.

CASE VI. Recently Priest and Alexander [3] reported a fifty-six year old woman who had had an islet cell tumor removed from the tail and body of the pancreas six years before death, because of abdominal pain. She had continued in good health until two years before death when epigastric pain, vomiting and jaundice developed; she underwent cholecystectomy and multiple gallstones were removed. Five or six months before death, severe intractable watery diarrhea developed with anorexia, occasional vomiting and weight loss. On admission to the hospital at that time she was found to have profound hypokalemia and hyponatremia. Laparotomy was carried out and no abnormalities were found at operation. She continued to do poorly, with more severe diarrhea and electrolyte derangements which improved after the administration of cortisone. On x-ray examination evidence of a shallow gastric ulcer was seen and a brisk hematemesis occurred, requiring cessation of cortisone therapy. Cortisone therapy was resumed in the terminal stages of her illness because of severe and uncontrollable diarrhea and electrolyte depletion. Again the diarrhea subsided until a further attempt at steroid withdrawal led to exacerbation and death four to five months after the onset of diarrhea. At autopsy the only finding described was a 5 by 5 cm. islet cell tumor in the tail of the pancreas which contained no beta cells. Approximately 1 per cent of the cells were alpha cells with small eosinophilic granules seen after appropriate staining. The tumor removed in 1949 was a similar islet cell adenoma.

CASE VII. Donaldson et al. [6] reported on a thirty-five year old man with severe watery diarrhea, abdominal cramps, nausea, vomiting, weight loss, hypochloremic alkalosis and tetany. No potassium

studies were recorded although one serum calcium was 10.7 mg. per cent. Surgical exploration became necessary four years after the onset of the diarrhea because of jejunal perforation. The resected jejunum contained four peptic ulcers. Very large volumes of acid gastric juice were obtained by suction. He progressively deteriorated and died on the eighth post-operative day. At autopsy masses were found in the head and tail of the pancreas measuring 3 by 4.5 cm. and 1 by 1 cm. respectively. The tumors were made up of islet cells but no specific granules could be identified. One peripancreatic lymph node contained well differentiated islet cell carcinoma. Multiple peptic ulcers were seen in the stomach and duodenum. A 9.5 mm. chromophobe adenoma of the pituitary was present. The kidneys showed only minimal nephrocalcinosis.

CASE VIII. Forty and Barrett [7] described a fifty-five year old woman with persistent diarrhea. One year after the onset of her diarrhea, which was severe enough to require hospitalization, she first noted pain in the epigastrium after meals. A few months later she began to vomit occasionally. A barium meal examination showed no abnormality. A couple of years later the severe epigastric pain and the passage of tarry stools prompted a further barium meal examination which showed dilatation of the second part of the duodenum and stricture of the third part. At exploratory laparotomy an adenocarcinoma of the head of the pancreas a few cm. in diameter was found. She died one month later, having gone into shock after a bout of severe abdominal pain. An autopsy revealed fresh ulcers at the gastrojejunal stoma, one of which had perforated. Two small islet cell adenomas were discovered in the pancreas. No cytochemical studies were made.

CASE IX. Gordon and Olivetti [8] reported on a twenty-six year old man who had a history of diarrhea, anorexia and weight loss followed by upper abdominal pain. A few days after admission to the hospital he had massive hematemesis and was treated with a bland diet and transfusions. During the following months a massive right pleural effusion developed from which 5,000 cc. of blood was aspirated. He had several episodes of shock as a result of repeated bleedings into his right pleural cavity and died after another such episode. No blood sugar or potassium determinations were recorded. At autopsy multiple perforations of the esophagus were seen and there was a 4.5 by 3.5 cm. adenoma in the tail of the pancreas. The cellular pattern of the adenoma resembled that of an islet cell adenoma but no cytochemical studies were carried out.

#### COMMENTS

The two cases herein reported and the seven cited from the literature emphasize the frequency with which diarrhea may be associated

with non-insulin-secreting islet cell tumors of the pancreas. The explosive watery diarrhea was the most difficult clinical problem in the two cases reported. Priest and Alexander [3] found that the diarrhea seemed to subside in Case VI after cortisone administration. We observed a similar short-lived improvement in Case II after hydration and electrolyte replacement. In no instance was a satisfactory clinical explanation of the diarrhea found in the nine cases reviewed. The unexpected discovery and surgical resection of an islet cell tumor in Case VIII described by Forty and Barrett [7] brought about clinical recovery with disappearance of the diarrhea.

Severe hypokalemia was well documented and persistent in Cases I and II and in Case VI reported by Priest and Alexander [3]. The severity of the potassium depletion was reflected by the vacuolar changes in the renal tubules seen in Cases I, II and V [5]. Similar changes have been described in other potassium-depleted patients [9,10]. The constant fixed low specific gravity of the urine seen in Cases I and II were characteristic findings of hypokalemic nephropathy [10].

It is known that prolonged diarrhea may cause potassium deficiency and such a mechanism could well explain the hypokalemia seen in these patients. The possibility of a substance elaborated by the islet tumor cells being more directly involved in causing the diarrhea or hypokalemia cannot be excluded. The watery nature of the diarrhea is perhaps more compatible with increased production than malabsorption of gastrointestinal juices. Certainly extreme hypersecretion of gastric juice was present in Case VII described by Donaldson et al. [6]. It is possible that the tumor may put out some substance causing stimulation of gastrointestinal secretion. The absence of a defect in fat absorption in Case II would further strengthen the view that overproduction and not underabsorption of juices is the mechanism of the diarrhea.

The occurrence of refractory and recurrent peptic ulceration in patients with islet cell adenomas of the non-insulin-secreting type has been emphasized [1,2]. Ellison [2] reviewed nineteen such cases and added five of his own. Since then there have been reports of three additional cases [5,6,11], making a total of twenty-seven cases to date. Of these, five had severe diarrhea as an early and cardinal symptom, as pointed out in the review of the case reports. In the cases reported here, no evidence

of ulceration was discovered in the gastrointestinal tract either clinically or at autopsy. It is difficult to say whether peptic ulceration and diarrhea in relation to islet cell adenomas are merely separate expressions of a common determining secretion of the tumor or are more causally related. An attractive but as yet unsubstantiated possibility is that two different tumors of the islets may exist, one composed of alpha cells and the other of delta cells, each associated with a different clinical course; in the one peptic ulcers predominating, in the other diarrhea more in evidence.

The studies of the cellular nature of the tumors in the different cases reported on and in the cases studied here are of little help as they agree only in that the cells are not of the beta type. Reports of the presence of alpha cells in the tumors associated with peptic ulceration are difficult to assess particularly since Gomori, who had the opportunity to examine those from the cases of Ellison, regarded the cells present as having no specific granulation when examined by his methods [12]. It is well to remember that the methods used for the differentiation of the islet cells are notoriously capricious [13,14] and depend greatly on the time elapsing between death and fixation of the tissue. Clearly, precise and careful histological study is necessary before any serious attempt is made to associate any particular cell type with the predominance of peptic ulceration over diarrhea or vice versa.

The tetany and edema in Case II and in Case VII reported by Donaldson et al. [6] occurred in association with hypopotassemia and hypercalcemia, and deserve some comment. Black and Milne [15] observed no tetany in subjects moderately depleted of potassium when extracellular sodium and pH were kept normal. Fourman [16], using resins, produced a more profound potassium depletion in human subjects but extracellular acidosis was present. Tetany was noted in one individual after correction of the acidosis and sodium administration. Mader and Iseri [17] reported tetany in a patient with hypokalemia due to aldosteronism. Fourman and McCance [18], while observing a patient who was potassium-deficient secondary to renal acidosis, noted the occurrence of tetany as the potassium deficiency and acidosis were being corrected. The tetany persisted for some time after extracellular electrolyte balance had been restored and gradually subsided, suggesting that some change had occurred within the cells.

Engel et al. [19] reported two patients in whom tetany developed in association with hypokalemia as potassium chloride was administered. They attributed the tetany to hypocalcemia which was marked in one of the patients and minimal in the other. There are two reports in the veterinary literature relating the tetany seen in cattle grazing on winter wheat to an increased potassium/calcium ratio in the blood [20,21]. Potassium administration in these animals resulted in an increased tendency for tetany to develop whether calcium levels were low or normal.

The hypercalcemia seen in Case II and the concomitant hypophosphatemia led to an incorrect clinical diagnosis of hyperparathyroidism. Although the mechanism of the hypercalcemia is not known, it is of interest that two total twenty-four hour calcium excretions in the urine were only 40 and 82 mg. in June 1955, a time when the serum calcium level was 12.8 mg. per cent. Calcium retention has been observed [16] in human subjects during the recovery phase following severe potassium depletion and in rats depleted of potassium [22].

The finding of a pituitary adenoma, microscopic in size, in Case I and in the case reported by Donaldson et al. [6] recalls the descriptions of multiple adenomas of the endocrine glands which had been considered a pathologic rarity for years [23] but are now coming more to the notice of clinicians [4,24,25]. The recent report by Moldawer et al. [4] reviewed the twenty-eight cases in the world literature in which adenomas of the pituitary, pancreatic islets and parathyroids were found in association. It is interesting that of the twenty-eight patients he lists, seven of them had associated peptic ulceration and of the patients with ulcers all had parathyroid adenomas. There was no evidence clinically or pathologically of hyperinsulinism or peptic ulceration in the cases herein reported, and no parathyroid adenomas were discovered.

Whatever relationship may exist between pancreatic islet cell adenomas and peptic ulceration, certainly diarrhea is a prominent symptom in many patients with such tumors. Peptic ulceration, when present, appears considerably later than the diarrhea which, if untreated, may itself bring about death from potassium deficiency and renal failure. In only one case of the nine so far reported was surgical resection of an islet cell tumor carried out early enough to cause disappearance of the symptoms.

As diarrhea of a refractory type appears to be an early symptom in one-third of the cases of non-insulin-secreting islet cell adenomas of the pancreas so far reported in the literature, more attention should be paid to it as a possible presenting symptom. In the cases reported and reviewed here, diarrhea was the earliest symptom in all and in only five patients did peptic ulceration occur at a later date. In one of these patients [5] the peptic ulceration appeared while the patient was being given adrenal cortical steroids in heavy doses to control the diarrhea.

Recognition of the fact that refractory diarrhea and hypokalemia may result from an underlying islet cell adenoma of the pancreas should lead to earlier diagnosis and surgical treatment in these patients.

## SUMMARY

Two cases are reported of a fatal syndrome of refractory watery diarrhea, hypokalemia, and vacuolar nephropathy in association with non-insulin-secreting islet cell adenomas of the pancreas. Seven cases of a similar nature are reviewed. The therapeutic significance of early diagnosis and treatment of this clinical syndrome is stressed.

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# Long-Term or Maintenance Adrenal Steroid Therapy in Non-tropical Sprue

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**S**PRUE is a malabsorptive disorder of unknown etiology and varying severity with a tendency to run a protracted course. The cardinal malabsorptive defect is steatorrhea, and this is often accompanied by multiple defects involving the absorption of other foodstuffs, vitamins and electrolytes. Primary sprue is a disease in which there is no demonstrable organic lesion of the intestine or mesentery, whereas secondary sprue is due to organic disease of the gastrointestinal tract. Primary sprue, or idiopathic steatorrhea, may also be divided into the tropical and non-tropical forms. This division is based chiefly on geographical grounds but in addition there is some reason to believe that the tropical form is more easily reversible, less apt to exhibit hypocalcemic tetany, and more amenable to therapy with vitamin B<sub>12</sub>, folic acid or liver extract [1,2]. The incidence of tropical sprue is apparently dwindling, a trend which has been attributed to improved diets in the endemic areas. On the other hand, with the development of newer methods of investigation and diagnosis, it has been possible within recent years to recognize an increasing number of cases of non-tropical sprue. Whereas in the past the malady has been considered to be quite rare, impressive series are now being reported from widely scattered centers in temperate climates and it would appear that there is a direct relationship between the degree of interest in the disorder and its "regional" occurrence. The majority of these patients have responded to dietary measures together with liver extract, vitamin B<sub>12</sub> or folic acid. However, all students of sprue have encountered some patients with an intractable form of the disease which has failed to respond to the standard therapy. This group of chronically ill, emaciated and incapacitated persons has constituted the hard core of patients with sprue and has challenged investigators in the

field to seek newer and improved methods of therapy.

For many years the finger of suspicion has been pointed to adrenal cortical deficiency in this disease but there has been no sound evidence to support this view [3-5]. Nevertheless, with the advent of ACTH and cortisone it was inevitable that these agents be given a trial in the management of non-tropical sprue. Early experience with these agents in the treatment of sprue indicated that they were indeed beneficial and at times dramatic in their effects but relapses occurred when the drugs were discontinued [1,2,6-10]. Fear of complications led most investigators to recommend intermittent dosage, waiting for symptoms of relapse to appear before reinstituting therapy [2]. In modern medicine relatively few chronic diseases are treated in this manner and one might well imagine what would happen to a diabetic or cardiac patient treated with insulin or digitalis in intermittent dosage. It seems more rational to us to explore the hazards and possibilities of long-term or maintenance dosage of adrenal steroids in non-tropical sprue. This report concerns our experience with small oral maintenance dosage of cortisone, hydrocortisone and prednisone in the treatment of six patients with non-tropical sprue over a period of one year to six years. The excellent results have led us to recommend small oral maintenance doses of adrenal steroids in the treatment of severe intractable sprue.

## CASE REPORTS

**CASE I.** J. S., a forty-one year old white housewife, was first seen in 1947 when she had severe symptoms of sprue manifested by fatty diarrhea, weight loss, anemia and tetany. These symptoms persisted for six months and then abated following treatment with liver extract and vitamins. She remained in remission and, except for moderate anemia, felt well until June

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1950, one month after the birth of her second child. She then had a severe recurrence of sprue with weight loss of 40 pounds in three weeks. She was admitted to a hospital where she remained for one month and was given liver extract, vitamins and folic acid by injection. She gradually improved but two days after return to her home she relapsed again and was admitted to the Presbyterian Hospital on September 17, 1950. She responded to dietary measures plus vitamin B<sub>12</sub>, folic acid, vitamin D and calcium, and was discharged on October 4, 1950. Following discharge she failed to improve despite intensive therapy and it was necessary to readmit her to the hospital in January 1951. Since she had failed to respond to conventional measures for sprue, it was decided to institute a trial on cortisone. At the time, cortisone was available to us only for parenteral use. In order to reduce the possibility of a psychologically induced response to a new medication, for one week she was given an intramuscular injection of a placebo each day as a control. This was without effect and at the end of this period a regimen of intramuscular cortisone was begun, 200 mg. daily for two days, then 100 mg. daily. On the fifth day she began to improve. The diarrhea diminished, her appetite improved, and she began to gain weight. After a month of treatment with cortisone the dosage was tapered off and she was sent home without cortisone. After twenty days she suffered a severe clinical relapse with marked diarrhea and recurrence of all of her previous symptoms. Cortisone was then resumed and she again quickly responded and began to gain weight. Intramuscular administration of cortisone was then stopped and a placebo tablet resembling oral cortisone was administered. After twenty-one days she again relapsed, with severe diarrhea, and was quite ill. The administration of oral cortisone, which was now available, brought about a rapid remission in a dosage of 25 mg. twice daily. After six months the dose was reduced to 25 mg. once daily. This was apparently inadequate for she relapsed in nine days but improved when the dose was doubled. On June 2, 1952, cortisone was discontinued and within sixteen days she suffered a severe relapse, with weight loss and marked diarrhea. Oral cortisone was resumed with an almost immediate response. Subsequently, it was possible to reduce the daily dose of cortisone to 25 mg. daily without evident ill effect. When re-evaluated in July 1953, while receiving maintenance cortisone therapy, she was in optimum health and weighed 130 pounds, 40 pounds over her initial weight. Hypoalbuminemia, which had been present, had disappeared. The serum calcium level was normal despite the fact that she had stopped taking vitamin D and calcium supplements four months before (April 1953). The serum carotene level had risen to normal. X-ray pattern of the small intestine revealed considerable improvement. The oral glucose tolerance curve was still flat. She continued to take cortisone until December 1953 when she decided to stop taking it. When seen again in March 1954, she

felt well except for symptoms attributed to cystitis. At this time her serum carotene level had fallen to 28 gamma per 100 cc. She continued to have urinary tract symptoms and when admitted to the hospital for these in January 1955, she was again anemic, steatorrhea had recurred and the serum carotene level had fallen to 6 gamma per 100 cc. The interstitial cystitis was treated but failed to improve. Following discharge from the hospital in February 1955, she suffered a severe relapse of sprue and lost 40 pounds. She refused to take steroids because she feared that they had caused the cystitis. She was therefore given standard replacement therapy by her physician. A gluten-free diet had been advised but she found it difficult to follow. In October 1956, she underwent a vaginal plastic operation with repair of a cystocele. At that time she was anemic, had steatorrhea, and the serum carotene level had fallen to zero while the serum vitamin A level was considerably below normal. She was also 13 pounds below her optimum weight and she tired easily. She recovered well from the operation and was relieved of her urinary symptoms. Following discharge she had another severe recurrence of sprue. It was necessary for her physician to add prednisone to the therapeutic program for a time. She remained reluctant to resume long-term adrenal steroid therapy. When last seen in February 1957, she was 26 pounds under her optimum weight and reasonably happy with her condition, but it was evident that she had adjusted to a lower level of health and activity as compared with the optimum level achieved while taking cortisone.

CASE II. A. H., a seventy-four year old white widow, was first seen in April 1951, at which time she presented a history of non-tropical sprue dating to at least ten years before and documented by thorough study elsewhere in 1947. Therapy had consisted of crude liver extract, folic acid, multivitamins and a high caloric diet had been recommended. Despite these measures repeated blood transfusions were needed for persistent anemia. The symptoms of frothy diarrhea, anorexia, weight loss and flatulence persisted, with frequent periods of severe exacerbation. Finally, in October 1950, the patient was hospitalized and a regimen of intramuscular ACTH was begun. Within three to four days striking improvement had occurred and she had a normal-appearing bowel movement for the first time in many months. Treatment was continued in the hospital for three weeks and subsequently at home for an additional five weeks. The dose was gradually reduced from the initial 25 mg. every six hours until it was stopped. Within a week the patient was in relapse. She was readmitted to a hospital and ACTH therapy re-instituted, 25 mg. intramuscularly every six hours, and this was continued for three weeks. Upon discharge the injections were gradually discontinued and soon relapse had set in. In January 1951, the patient underwent exploratory laparotomy and appendectomy in

an attempt to clarify the diagnosis. The operative findings were consistent with primary sprue; nothing was found to suggest any organic lesion of the intestine, pancreas, mesentery or lymph nodes. She was discharged to her home. In April 1951 treatment with oral cortisone, 12.5 mg. every six hours, was instituted and she began to improve. It was necessary to increase the dose of cortisone to 25 mg. four times daily for two months, then it was decreased to 12.5 mg. four times daily and she then remained in a good remission. In December 1951, she was admitted to the Presbyterian Hospital for evaluation while in a phase of clinical remission. The findings indicated improvement in the oral glucose tolerance curve, which was now in the low normal range, and less severe steatorrhea than she had previously exhibited. The erythrocyte sedimentation rate was elevated. The cephalin flocculation and thymol turbidity tests were 3 plus, with a normal bromsulphalein<sup>®</sup> excretion test. Hepatomegaly, which had been present for years, was unchanged. The small bowel motor function by x-ray examination was severely deranged and consistent with sprue. In March 1952, cortisone was stopped but within forty-eight hours severe diarrhea appeared and it was necessary to resume it. She remained in remission until June 1952, when she attempted to reduce the cortisone to 12.5 mg. three times daily, and noted general malaise and abdominal discomfort. These improved after increasing the dose to 12.5 mg. four times daily. On April 21, 1953, the patient uneventfully underwent a pelvic plastic repair while under general anesthesia. Prior to the operation she was given ACTH intramuscularly for three days and the cortisone was then stopped. Two weeks after the operation cortisone was resumed for a recurrence of diarrhea and it was continued in the dosage of 12.5 mg. four times daily. In October 1954, she suffered a posterior myocardial infarction from which she recovered without sequelae. Cortisone was continued throughout this illness and the sprue was adequately controlled. In December 1954, she was advised to eliminate gluten from her diet in addition to continuing with the previous therapy. There was no additional clinical improvement attributable to the gluten-free diet. In February 1956, because of a recurrence of diarrhea which had required an increase in the cortisone dose to 25 mg. four times daily, it was decided to change to prednisone, 5 mg. twice daily. Her symptoms improved on this program and she has remained in good health, continuing prednisone, 5 mg. twice daily, ever since.

CASE III. L. S., a fifty-one year old white housewife, was first seen on October 4, 1951, at which time she complained of abdominal distress, vomiting, weakness and bouts of diarrhea with frothy, light-colored stools. These symptoms began about eleven years before and were accompanied by intermittent sore mouth, sore tongue, a resistant anemia, paresthesias of the fingers and marked fatigability. She

was treated at first with iron and given transfusions of whole blood. In addition, she received injections of liver extract with partial benefit but never with complete remission of her symptoms. She was told she had colitis. The liver injections were given for several months, three times weekly, then discontinued for several months, then resumed. The most recent course of liver injections was from October 1950 until June 1951, without any apparent benefit. She had lost weight steadily from her maximum weight of 118 pounds five to six years ago to her present weight of 87 pounds, the major portion of it during the preceding two years. She had never lived in the tropics. For a period in March 1951, she resided in Florida for one month.

On physical examination she appeared emaciated and pale but alert and pleasant. The tongue was beefy and fissured. The abdominal musculature was quite lax, a phenomenon commonly encountered in adult sprue. There were no other unusual physical findings. The laboratory findings were those of severe sprue and consisted of steatorrhea, a zero serum carotene level, prolonged prothrombin time, moderate anemia, hypoalbuminemia and a flat oral glucose tolerance curve. The roentgen pattern of the small intestine was that of severe sprue. The patient was admitted to the hospital on October 7, 1951, and was discharged November 10, 1951. Therapy was initiated with a special diet, oral folic acid, parenteral vitamin B<sub>12</sub> and oral multivitamin supplements. There was no apparent response to these measures and since there was also a history of lack of response to liver extract injection and vitamin B<sub>12</sub> in the past, it was decided to add cortisone to the usual measures. The response was dramatic as evidenced by cessation of diarrhea, improvement in strength and appetite, and laboratory evidence of improvement. The anemia proved, on analysis, to be an iron-deficiency type and treatment with intravenous iron was given with an excellent response. She was discharged on a regimen of cortisone 25 mg. twice daily, folic acid 5 mg. three times daily, a multivitamin capsule three times daily, an oral crude liver extract 15 cc. three times daily, and vitamin B<sub>12</sub> 30 gammas intramuscularly twice weekly. The diet was high in protein, moderately low in fat and high in calories, distributed in six feedings. She had gained 13 pounds since initiation of cortisone therapy. She was followed up regularly as an outpatient and continued to improve. By January 1952, she weighed 114 pounds, only 5 pounds under her previous maximum weight, and she felt perfectly well. At this time the dose of cortisone was reduced to 12.5 mg. twice daily, but within a week slight diarrhea recurred for the first time since initiation of therapy with cortisone and she tired more easily. The dosage of cortisone was therefore increased to 25 mg. twice daily, and the diarrhea quickly disappeared and she again felt very well. Despite excellent clinical remission, in April 1952, laboratory evidence of sprue remained essentially unchanged except for

the blood count which was perfectly normal (hemoglobin 14.4 gm. per cent, red blood cells 4.72 million per cu. mm.). The oral glucose tolerance curve remained flat, the stool microscopic fat test was still strongly positive. The serum carotene had risen to 16 gamma per 100 cc. but was still below the normal level of at least 40 gamma per 100 cc. X-ray findings of the small intestine had, however, shown striking improvement.

On April 3, 1952, the dosage of cortisone was reduced to 12.5 mg. twice daily, and three weeks later, since there had as yet been no relapse, cortisone was stopped, but the remaining measures were continued. After approximately one month the patient noted slightly increased fatigability, slight abdominal distress, and flatulence and loss of appetite. On July 11, 1952, because of epigastric discomfort, nausea, anorexia and slight weight loss (but no diarrhea), she resumed cortisone 25 mg. twice daily and noted a gradual improvement in strength and appetite. The nausea and abdominal distress rapidly cleared and she continued to take cortisone, 25 mg. twice daily, until September 3, 1952, when the dosage was again reduced to 12.5 mg. twice daily, and later, on October 6, 1952, it was again discontinued. Within two weeks a recurrence of diarrhea, weight loss, flatulence and fatigability developed. The diarrhea and fatigability became progressively worse and soreness of the tongue appeared. Despite this, cortisone was not resumed until December 1, 1952, at which time 25 mg. twice daily was reinstituted. It took about one week to initiate a remission and on January 12, 1953, the dose was reduced to 12.5 mg. twice daily. This dose proved inadequate to maintain an optimum clinical remission and it was necessary on February 13, 1953, to increase the dose once again to 25 mg. twice daily. It was concluded by this time that the optimum dose of cortisone for this patient was 25 mg. twice daily. On March 16, 1953, hydrocortisone was made available and it was decided to try this agent in the dosage of 20 mg. twice daily. The patient thought she felt better while on hydrocortisone than on cortisone, but this is difficult to evaluate. During May and June 1953, while she was taking hydrocortisone and in clinical remission, laboratory studies were repeated. The steatorrhea and low carotene level persisted. The oral glucose tolerance test was slightly improved. The blood count was normal. The small intestine motor function appeared slightly deranged but by no means as severely as in the original examination of October 1951. The patient is still receiving hydrocortisone, the dose varying between 10 mg. twice daily and 20 mg. twice daily, and she has remained in excellent general health.

CASE IV. H. H., a forty-three year old white Canadian housewife and former registered nurse, was referred by her physician on November 24, 1954, because of severe and intractable non-tropical sprue.

The onset of her illness was in October 1951 with severe watery diarrhea and abdominal cramps. These symptoms responded temporarily to symptomatic measures only to recur intermittently. The stools became very bulky, greasy and greyish yellow in color. She did not seek medical advice until August 1952 when, because of persistent diarrhea and marked weight loss, she was admitted to a hospital where complete studies were performed. The radiologist suggested that she had sprue and therapy with folic acid and vitamins was begun but she failed to respond. Pancreatogenous steatorrhea was suggested as the diagnosis at this point but there was no laboratory support for this view and no sustained response occurred to full dosage of pancreatic extract. A brief trial of cortisone, a total of twelve tablets, 25 mg., over a one-week period produced temporary improvement in the diarrhea. However, the medication was not continued because of fear of complications. She continued to lose weight, from her average of 130 pounds to 110 pounds, and diarrhea was severe and persistent. In December 1952, she was admitted to the Montreal General Hospital where the diagnosis of sprue was confirmed. Laboratory studies at that time included a six-day fat balance determination. On a daily diet containing 75 gm. of fat and 70 gm. of protein, the patient excreted 42 gm. of fat per day, while the fecal nitrogen excretion was only 1.85 gm. per day. The patient was treated with a special diet and vitamin supplements. She improved and was discharged on December 23, 1952. During January and February 1953, her condition became worse. On March 2, 1953, she was admitted to the Montreal General Hospital in a dehydrated critical state, having lost 30 pounds. She was given ACTH, 25 mg. intravenously, daily for eight days. She was also transfused, given vitamin supplements and a wheat-free diet. The response was dramatic, she gained nearly 30 pounds and had a ravenous appetite. She remained well all of that year except for the persistence of huge, bulky stools once daily and the phenomenon of nocturnal diuresis [2]. Her weight had risen from a low point of 80 pounds to 108 pounds where it remained, still well below her average weight of 130 pounds. In February 1954, because of recurrence of diarrhea, she was given cortisone for ten to twelve days, with a prompt response. The cortisone was then stopped and resumed whenever she had a relapse. In June 1954, she experienced a severe bout of diarrhea and a regimen of 100 mg. of cortisone daily was begun, the dose being quickly reduced to 25 mg. daily; the latter dose failed to control the diarrhea. On August 14, 1954, she was again admitted to the Montreal General Hospital and given a short course of cortisone over a ten-day period and was discharged on September 4, 1954. She was home for two days when she noted severe gnawing epigastric distress radiating to the back. This pain was periodic and responded to alkali or food. On September 11, 1954,

when taking an afternoon nap, she was awakened by excruciating epigastric pain followed by vomiting which seemed projectile. The pain persisted and on September 14, 1954, she was taken to a hospital in Montreal. Intravenous ACTH was given and she improved rapidly. After four injections she was given 100 mg. of cortisone daily for two days, 75 mg. for two days, 50 mg. for two days, then 25 mg. daily for twenty-five days. It was then stopped. She was sent home on October 23, 1954, only to suffer another recurrence of sprue on November 3, 1954. This became so severe that it was necessary to admit her to the Brockville, Ontario, Hospital on November 14, 1954. There she was given 25 mg. of ACTH intravenously daily for six days and this was followed by 100 mg. of cortisone each day. When admitted to the Presbyterian Hospital in New York City on November 24, 1954, she was taking 75 mg. of cortisone daily. She appeared chronically ill and weighed only 100 pounds. The laboratory findings were those of classic non-tropical sprue. X-ray of the small intestine revealed severe change and in addition there was evidence of a duodenal ulcer with a crater at the apex of the duodenal cap. Despite the presence of the ulcer, it was decided to proceed with maintenance adrenal steroid therapy using hydrocortisone, 10 mg. four times daily. In addition, the previously instituted measures of a gluten-free diet, folic acid, vitamin B<sub>12</sub> and calcium lactate were continued. Aluminum hydroxide-magnesium trisilicate gel was given for the ulcer. The response was dramatic and on the day of discharge, December 14, 1954, the patient felt much improved, had no diarrhea, and weighed 109 pounds. Nocturnal diuresis persisted during the period of hospitalization. The patient returned to her home in Canada and reported to me at regular intervals. Her progress was excellent and she suffered no relapses. On October 16, 1955, she returned to the Presbyterian Hospital for a check-up. At this time she looked the picture of good health, and weighed 148 pounds, a gain of 48 pounds since initiation of maintenance adrenal steroid therapy. The combined X-ray study of the gastrointestinal tract and small intestine revealed complete healing of the duodenal ulcer and the small bowel pattern appeared normal. Fat absorption tests using I<sup>131</sup>-tagged olive oil and oleic acid revealed nearly normal absorption of these substances. The serum carotene level had risen from zero to 32 gamma per 100 cc., the normal level being 40 gamma or more per 100 cc. The oral glucose tolerance curve, however, was still abnormally flat. The phenomenon of nocturnal diuresis had disappeared. On October 22, 1955, the patient was discharged from the hospital and advised to continue with the same program. She has continued to remain in excellent health while taking 10 mg. of hydrocortisone twice daily.

CASE V. R. C., a forty-three year old white housewife, was seen on December 30, 1955, at the request

of her husband, a physician. Her history of sprue had its onset in 1942 when frothy diarrhea and heartburn developed. The distress was relieved by alkali but the frothy diarrhea persisted for some months and then subsided. In 1947, eighteen months after the delivery of a normal infant, she had diarrhea, anorexia, weight loss, tetany, sore tongue and edema of the feet. She was treated with crude liver extract and vitamin B-complex by injection and she improved. In 1950 her symptoms recurred and a complete diagnostic study was performed which revealed a flat oral glucose tolerance curve, and steatorrhea; X-ray pattern revealed a markedly abnormal small intestine. The diagnosis of sprue was made and she was treated with folic acid and crude liver injections. She improved and continued in a fair remission until September 1955 when severe diarrhea developed; she lost ten to fifteen pounds and failed to respond to liver extract, folic acid and intramuscular injections of vitamins. She also had severe tetany with a serum calcium level of 7.3 mg. per cent. Massive edema then appeared, due to hypoalbuminemia, the serum albumin level having fallen to 1.9 gm. per 100 cc. She was admitted to a hospital on October 20, 1955, and given 25 gm. of concentrated human serum albumin intravenously and 500 cc. of whole blood. Within a matter of several hours diuresis ensued and she lost most of the edema. On October 22, 1955, she was given another unit of human serum albumin intravenously. At this juncture she weighed 85 pounds, 20 pounds under her average weight. On October 25, 1955, a regimen of prednisone was begun, 30 mg. the first day, 25 mg. the second day, 20 mg. the third, 15 mg. the fourth day, and the dose was progressively reduced until it was stopped on November 5, 1955. The diarrhea, which had persisted during the diuresis, subsided rapidly after the initiation of steroid therapy and the serum albumin level had risen to 4.1 gm. per 100 cc. on November 8, 1955. She was discharged from the hospital on November 12, 1955. On November 19, 1955, diarrhea recurred; it was of great severity and the stools were very foul. On November 25, prednisone was resumed in the same dosage as before. By November 30, the stools were formed but tetany had reappeared, requiring intravenous and oral calcium for control. On December 5, therapy with prednisone was stopped. By December 12, ankle edema had recurred and by December 14, it was quite severe. She continued to do poorly, had severe diarrhea, anorexia and weakness. On December 27, 1955, the prothrombin time had risen to fifty seconds, the serum proteins remained normal but the serum calcium was 8.4 mg. per 100 cc. When first seen by me on December 30, 1955, she was extremely discouraged and sick. She appeared emaciated, pale and chronically ill. She refused to consider entering a hospital again and it was decided to institute long-term prednisone therapy. Prednisone therapy was begun, 5 mg. four times daily, and she was advised to continue taking vitamin supplements, folic

acid, vitamin D and calcium. The response was striking. The diarrhea cleared rapidly and her appetite returned as did her general strength. Neither tetany nor edema occurred. She was subsequently given a gluten-free diet which she tolerated well. By March 22, 1956, she had gained 30 pounds and appeared to be in excellent health. The prednisone dose was gradually reduced to 5 mg. daily. When last seen on June 5, 1957, she appeared to be perfectly well. She continues to take prednisone, 5 mg. daily.

CASE VI. D. L., a forty year old housewife, had sprue in 1950 and failed to respond to conventional therapy. In 1954 she was admitted to a hospital and after thorough diagnostic study cortisone therapy was started. She was advised to take this for several weeks and then gradually taper off and stop. However, she relapsed after several weeks and she then resumed the cortisone with resulting improvement. She had been warned not to take cortisone continuously but soon noted that she would relapse without it, only to improve quickly while taking it. Her course consisted of many ups and downs and she was quite discouraged when first seen in August 1956 at the Presbyterian Hospital. The laboratory and clinical findings were those of severe sprue in relapse manifested by cachexia, edema, hypoprothrombinemia, hypocalcemia, hypoalbuminemia, anemia, steatorrhea and a flat oral glucose tolerance curve. Therapy with prednisone was instituted with a splendid response. She is now taking prednisone, 5 mg. once daily, and has been in optimum health.

#### COMMENTS

The rapid response of these six patients to adrenal steroid therapy has been paralleled by our observations in a similar number of patients whom we have not been able to follow up quite as closely. One additional patient, for reasons unclear to us, failed to respond to this form of therapy.

The beneficial effects of therapy have consisted of marked improvement in stamina and appetite, cessation of diarrhea, striking weight gain and disappearance of tetany. Rises in serum albumin have been impressive and, when studied, the absorption of fat from the intestine has been much improved [17]. X-ray pattern revealed a marked improvement in the small bowel after some months. There have been no adverse effects attributable to this form of treatment in these patients. X-ray findings of the chest remain within normal limits and there has been no evidence of diabetes or hypertension despite years of continuous steroid therapy. In one patient, an active duodenal ulcer developed, then healed completely in the course of long-

term hydrocortisone therapy. Another patient underwent exploratory laparotomy without ill effects and three years later survived a posterior myocardial infarct without difficulty while on long-term cortisone therapy for sprue. There has been no evidence of compression fractures of the spine or progression of osteomalacia as a result of this therapy. These patients appear to be perfectly well and are able to work and perform their duties as healthy vigorous human beings. (Table I.)

That this happy sequence is not universal is seen from our experience with an additional patient who was the very first one that we treated with cortisone. This was a twenty-seven year old white housewife with severe intractable sprue who, in October 1950, was given cortisone for only six weeks and responded favorably with a weight gain of 30 pounds. She later had homologous serum hepatitis following a transfusion and became gravely ill and febrile. An enlarged lymph node was noted in the right anterior cervical chain and when it was excised it proved to be tuberculous. A course of streptomycin was given with temporary improvement. Subsequently, severe sprue recurred and, despite repeated warnings and against our advice, maximal dosage of ACTH and cortisone were given to the patient by her family physician. The patient failed to respond and ultimately died of disseminated tuberculosis, despite chemotherapy. Although severe malnutrition secondary to intractable sprue and hepatitis might alone have been responsible for this sequence of events, one cannot escape the conclusion that cortisone and ACTH may well have contributed to this fatality.

Despite this single adverse experience which was not in a patient on long-term therapy, the evidence is overwhelming that adrenal steroids have a beneficial effect in the treatment of severe sprue [1,6,7]. Granted this, what is the evidence in favor of long-term steroid therapy of this disease rather than intermittent short courses? From the protocol of J. S. (Case I) it is evident that relapse occurred on the three occasions when cortisone was stopped during the first eighteen months of her treatment period. These relapses were not immediate but occurred twenty days, twenty-one days and sixteen days after discontinuance of cortisone. Similarly, in L. S. (Case III) relapse occurred about one month after stopping cortisone and on a later test, two weeks after cortisone was discontinued. In H. H.

TABLE I  
EFFECT OF ADRENAL STEROID THERAPY IN SPRUE

Data	Weight (lb.)	Hemo- globin (gm. %)	Stool Fat	Serum Determinations							Pro- throm- bin Time (sec- onds)	Glu- cose Toler- ance Curve	X-ray of Small Intes- tine
				Carotene (gamma/ 100 cc.)	Vitamin A (units/ 100 cc.)	Choles- terol (mg. %)	Albu- min (gm. %)	Glob- ulin (gm. %)	Ca (mg. %)	P (mg. %)			
Case I, J. S.													
Before Therapy:													
Feb. 1951.....	90	10.3	4+	0	72	117	3.2	2.4	6.8	1.0	21	Flat	4+
After Therapy:													
Oct. 1951.....	120	6.9	3+	0	80	147	4.1	1.9	10.3	3.3	..	.....	...
July 1953.....	130	11.0	4+	54	159	...	4.3	2.1	10.2	3.4	15	Low	2+
Stopped Therapy:													
Dec. 1953.....													
Mar. 1954.....	129	13.7	4+	28	63	...	4.2	2.1	10.2	...	19	.....	...
Jan. 1955.....	126	10.5	4+	6	133	...	3.7	2.0	9.5	3.8	17	.....	...
Oct. 1956.....	117	9.7	3+	0	46	...	.....	.....	.....	...	21	.....	...
Case II, A. H.													
Before Therapy:													
Apr. 1951.....	95	9.8	4+	0	88	200	4.0	3.4	9.4	3.2	..	Flat	4+
After Therapy:													
Dec. 1951.....	115	11.2	4+	0	50	196	.....	.....	.....	...	21	Low	4+
Case III, L. S.													
Before Therapy:													
Oct. 1951.....	87	7.1	4+	0	72	...	2.7	2.0	10.0	2.5	28	Flat	4+
After Therapy:													
June 1953.....	112	12.5	4+	14	113	180	3.5	2.9	9.8	3.1	17	Low	2+
Oct. 1955.....	120	12.0	4+	38	56	187	3.3	1.9	10.0	3.1	16	Flat	1+
Sept. 1957.....	114	10.3	1+	32	91	242	3.9	2.1	.....	...	18	.....	...
Case IV, H. H.													
Before Therapy:													
Nov. 1954.....	100	11.8	4+	0	116	170	3.8	1.9	9.0	2.7	16	Low	4+
After Therapy:													
Oct. 1955.....	148	13.3	1+	32	81	213	4.0	3.1	.....	...	13	Flat	2+
Case V, R. C.													
Before Therapy:													
Sept. 1955.....	86	13.0	4+	..	...	368	1.96	0.84	7.3	2.9	50	Flat	4+
After Therapy:													
June 1957.....	117	12.5	...	13	193	290	4.29	1.31	10.2	3.1	14	.....	...
Case VI, D. L.													
Before Therapy:													
Aug. 1956.....	106	7.4	4+	0	50	91	2.2	2.3	6.2	2.9	45	Flat	4+
After Therapy:													
Sept. 1956.....	150	13.0	...	..	...	168	2.2	3.5	9.1	3.1	14	.....	...
Aug. 1957.....	144	14.7	0	16	85	211	4.0	2.2	10.4	3.2	15	Normal	2+

(Case iv) the protocol is replete with repeated relapses following intermittent therapy with ACTH and cortisone. These, too, appeared two to three weeks after therapy had been stopped. The result was numerous acute episodes of severe sprue with depletion of electrolytes and dehydration necessitating repeated emergency hospital admissions. Her course since initiation of long-term continuous hydrocortisone therapy in November 1954 has been one of steady progress and optimal good health. Similar evidence accrues from R. C. (Case v) and D. L. (Case vi) whose need for maintenance prednisone therapy seems evident from their protocols. The oldest patient of the series (A. H.), now seventy-four years of age, has reacted so violently to reduction of the dose of cortisone that we have not dared to interrupt her therapy for any prolonged period since its inception in April 1951 except for the period of the pelvic plastic operation in 1953. At this time, two weeks after stopping cortisone, she relapsed but responded well to resumption of oral cortisone.

These observations would seem to establish clearly the need for long-term adrenal steroid therapy in these patients with severe sprue. The daily amount required for maintenance has been remarkably constant for each person and has not exceeded 50 mg. of cortisone, 40 mg. of hydrocortisone or 10 mg. of prednisone, and has usually been lower. The objection to prolonged therapy is that it may invite certain complications. These may consist of reactivation of tuberculosis (as occurred in one patient herein cited), development of peptic ulcer or diabetes, progression of osteoporosis or suppression of adrenal function. With the one exception noted, these complications have not occurred in the admittedly small number of cases reported. On the contrary, the general health of these patients has been much improved and they have been spared the hazards of intermittent therapy which is dependent upon the occurrence of a relapse for initiation. One patient (J. S.) who stopped taking cortisone after nearly three years of continuous therapy seemed to suffer no immediate adverse effects. However, one year after stopping it, her symptoms recurred and recently she has needed prednisone in order to control her disease.

It is not proposed that all patients with sprue be given long-term adrenal steroid therapy. This should be reserved for those patients with intractable sprue who have failed to respond to

the standard measures of special diets, vitamins, folic acid and vitamin B<sub>12</sub> or liver extract. Furthermore, even the patients with intractable sprue should have a trial on a gluten-free diet before resorting to long-term steroids. We have exercised care in excluding from steroid therapy any patient suspected of having active tuberculosis. We have also avoided this form of therapy in patients with considerable emotional instability. However, at times a short course of corticotropin or adrenal steroids has been used to control a "crisis" of sprue even in patients thought to be unsuited for long-term or maintenance therapy.

#### MECHANISM OF ACTION OF ADRENAL STEROIDS IN SPRUE

The mechanism whereby adrenal steroids exert their beneficial effects in non-tropical sprue remains obscure. The findings of hypotension, skin pigmentation, hypoglycemia and diminished urinary 17-ketosteroids have been among those directing attention to the adrenal cortex in this disorder. Thaysen [12] in his excellent monograph failed to find any evidence of adrenal cortical disease in his autopsy material of patients with non-tropical sprue. The disturbances of serum electrolytes encountered in sprue, hyponatremia and hypokalemia, were found to be due to fecal losses of these substances [13,14] and not to be influenced by desoxycorticosterone acetate [15]. Paniagua et al. [4] studied adrenal function in tropical sprue and concluded that the cortical reserve was normal in this disease. However, Diéz Rivas et al. [5] reported what they regarded as evidence of adrenal cortical deficiency in patients with tropical sprue, basing their conclusions upon low twenty-four-hour urinary 17-ketosteroid values, abnormal Kepler water tests and Cutler-Wilder tests, and abnormal Thorn tests. These findings are non-specific and may occur in many chronic diseases. The Kepler water test and the Cutler-Wilder test are invalidated as measures of adrenal function in sprue because of impaired water and electrolyte absorption from the intestine. The adrenal sections in thirteen autopsied cases of tropical sprue were reported by Diéz Rivas et al. [5] to exhibit changes consisting of "depletion of cortical lipids, cellular atrophy of the zona glomerulosa and the zona fasciculata, edema of the interstitial tissue of the atrophied parts and occasional focal infiltration of the cortex and medulla with cells resembling lymphocytes." These changes also are non-specific and have

been found in many conditions associated with malnutrition [8].

To the best of my knowledge, Almy's [9] patient was the first with intractable sprue to receive ACTH, in June 1950. The results were encouraging. Nearly simultaneously, Taylor, Wollaeger and Comfort [6] reported good results in sprue treated with cortisone. Their balance studies indicated that cortisone improved the intestinal absorption of fat and depressed the fecal loss of nitrogen. Similar results have been reported by other observers [7,8,16,17].

Despite the abundance of reports of the beneficial effects of adrenal steroids in this disease, no one has been able to put forth a valid explanation of the mechanism involved. It is difficult to accept the theory that distinct adrenal cortical insufficiency is present in sprue. If this were the case, one would expect to see full-blown sprue in at least some patients with Addison's disease, but this is rarely if ever encountered [18]. Christy [19] has studied the blood steroid levels of several of our patients with sprue before and after the intravenous injection of 25 mg. of ACTH. The findings have been within normal limits, arguing for an intact adrenal gland. It would seem that in the present state of our knowledge the most that can be said regarding the response to adrenal steroids of the patient with non-tropical sprue is that these hormones, in some unknown manner, appear to influence the absorption of various substances from the small intestine. The actual mechanism involved is hypothetical and it remains for further study to clarify its nature.

Before concluding this discussion, something must be said concerning the role of wheat gluten in sprue [20]. It appears that in celiac disease, at least 50 per cent or more of the patients are benefited by eliminating the gluten of wheat, rye and oats from their diets. Similar results have been reported in adults [21-23]. Our own limited experience indicates that gluten intolerance may be implicated in perhaps one of three adults with non-tropical sprue. The best responses in our patients have occurred in adults who had a history of childhood celiac disease. It is of interest that none of the patients in the present series who were treated with adrenal steroids had a history of childhood celiac disease. The mechanism of action of the gluten-free diet remains conjectural. It appears to be one of a number of trigger mechanisms which may be responsible for malabsorption. It is conceivable that it

exerts its influence through an inborn or acquired error of metabolism involving the disposal of glutamine, the chief amino acid constituent of gluten. The degree of sensitivity seems to differ from patient to patient and may vary considerably in the same patient. At times the acuteness and violence of the gluten-induced symptoms suggests an allergic reaction. If this were the case, the efficacy of adrenal steroids is understandable. Some of the abnormal roentgenological findings in the small bowel in sprue have been attributed to excessive secretion of mucus [24]. Perhaps gluten may stimulate excessive activity of the mucus-secreting cells of the small intestine. Further study of the gluten sensitivity phenomenon is under way in the hope that light will be shed upon the basic mechanisms involved.

#### SUMMARY

1. Low dosage long-term or maintenance adrenal steroid therapy is recommended for the management of selected patients with severe, intractable sprue.
2. Six patients with severe non-tropical sprue have responded well to this form of therapy.
3. These patients require a small maintenance dose of adrenal steroids in order to maintain optimum health and will relapse if this dose is reduced or discontinued.
4. Despite prolonged therapy (over six years in one case), no adverse effects have been detected in these patients.
5. The mechanism of action of adrenal steroids in sprue is discussed.

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# Peroral Small Bowel Mucosal Biopsy\*

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ADEQUATE material for the histologic study of the small intestine in man is difficult to obtain because of the changes produced by handling, by the clamping of blood vessels when surgical material is obtained and by autolytic changes when postmortem material is employed. Specimens of gastric mucosa can be taken by the Wood [1] instrument and duodenal or upper jejunal mucosa by the Shiner tube [2]. Since these are peroral technics which do not require anesthesia, manipulation or clamping of the organs, and since fixation is accomplished seconds after the tissue is removed, excellent histological preparations can be made.

An intestinal biopsy capsule has recently been developed at the Walter Reed Army Institute of Research [3] which makes it possible to obtain biopsy specimens from any part of the intestinal tract without laparotomy and to fix them promptly. The procedure may be repeated as frequently as necessary. The patient is comfortable throughout the entire period.

The intestinal biopsy capsule† is an ovoid, metal, hollow chamber, 17 mm. long and 11 mm. in diameter. (Fig. 1.) It is perforated on one side and contains a spring-actuated cutting blade, an air chamber, and a diaphragm. Polyethylene tubing (size 200) enters the capsule at one end and serves as a means of triggering the knife as well as a means of recovering the instrument after the specimen has been taken. Suction applied to the free end of the tubing is transmitted to the capsule, causing intestinal mucosa to be pulled into the apparatus, thus occluding the biopsy port. Air in the chamber expands and moves the diaphragm which causes the knife to be tripped and the mucosal specimen to be cut free.

† Obtained from College Park Instruments, Box 73, College Park, Md.

\* From the Walter Reed Army Hospital and Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

## BIOPSY TECHNIC

The instrument should be kept clean and the cutting blade and spring protected by a thin coating of stop-cock grease. Sharp knife blades must be used. The instrument is assembled and the knife blade cocked. Any desired length of

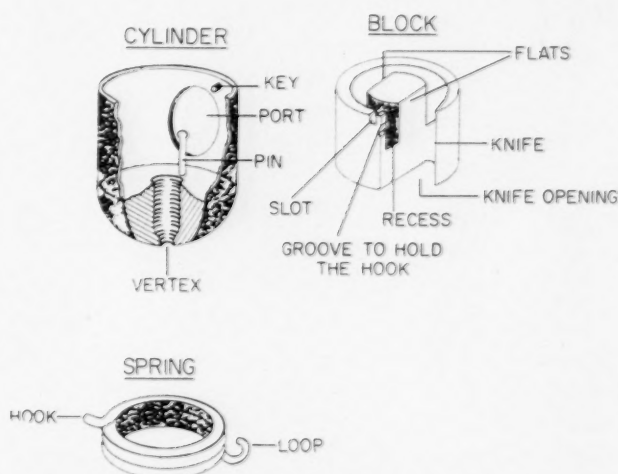


FIG. 1. Intestinal biopsy capsule disassembled. Air chamber and diaphragm are not shown.

polyethylene tubing may be used. Five feet is enough to reach into the jejunum, but we have employed as much as 15 or 20 feet to reach the ileum. The free end of the tubing is clamped in order to avoid regurgitation of intestinal contents through the tube. Two or more capsules may be used at once with the several tubes taped together. (Fig. 2.) The patient swallows the capsule, using water or gelatin to facilitate its passage into the esophagus. The customary maneuvers are then employed to pass it through the stomach and into the desired part of the intestine. Location of the capsule is established by calibration of the tubing. Before attempting to cut the specimen, the tubing and capsule

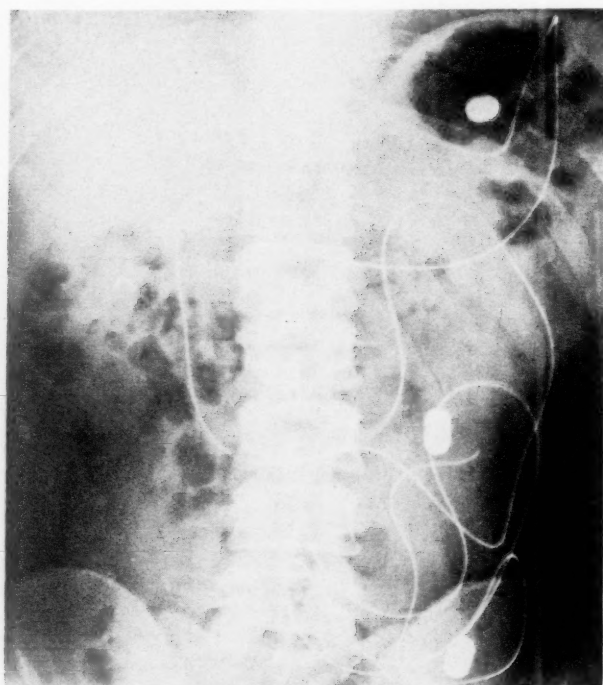


FIG. 2. Roentgenogram of a subject after swallowing three biopsy capsules simultaneously. Radiopaque material has been instilled into control tubing of one capsule.

should first be flushed with 10 ml. of normal saline solution, and then filled with air. Then, suction is applied two or three times for several seconds each. If fluid returns, it is an indication that the biopsy port is still open and it may be necessary to withdraw the instrument a few centimeters and try again. The patient may lie prone or sit erect as the instrument is withdrawn; resistance is encountered at the pylorus and at the cardia, but this is overcome by gentle traction while the patient swallows a bit of water. The instrument is taken apart and the

specimen removed for fixation or such special handling as may be appropriate.

During the period of development of the instrument, failure to obtain a specimen occurred in one-third of our attempts. At present our failure rate is about 10 per cent. The reasons for failure were: (1) difficulty in swallowing the instrument, or in securing its passage into the desired location; (2) failure of the instrument to "fire," which is almost always due to occlusion of the tubing by food particles, thick mucus, kinking of the tubing, or to jamming of the moving parts and; (3) occlusion of the port by mucus or food explains those occasions when everything goes as it should, but no specimen is found when the capsule is opened. Test "firing" the instrument before it is used and filling the capsule with air just before suction is applied seem to be important in reducing the number of failures.

The results of our initial attempts with this instrument are summarized in Table 1. Sixty-three attempts to obtain biopsy specimens have been made in thirty-eight persons, with twenty-two failures. Thirty-three of the forty-one specimens came from the jejunum, two from the ileum, and one from the stomach. The five esophageal biopsies were not intended, but occurred when the operator thought that the instrument was in the stomach. Untoward sequelae have not been experienced.

#### THE BIOPSY SPECIMEN

The specimen removed (Figs. 3, 4, 5 and 6) consists of a small disk of mucosa measuring, if all proper conditions have been met, approximately 7 mm. in diameter. Since 10 to 100

TABLE 1  
INTESTINAL BIOPSY CAPSULE—PERORAL INTESTINAL BIOPSIES

Clinical Diagnosis	No. of Patients	Biopsy Attempts	Failures	Tissue Removed			
				Esophagus	Stomach	Jejunum	Ileum
Normal . . . . .	6	14	4	4	..	5	1
Malabsorption syndrome . . . . .	4	12	4	..	..	8	..
Regional enteritis . . . . .	4	4	2	..	..	1	1
Hodgkin's disease . . . . .	7	11	3	..	..	8	..
Pernicious anemia . . . . .	3	6	3	1	1	1	..
Other diseases . . . . .	14	16	6	..	..	10	..
Totals . . . . .	38	63	22	5	1	33	2

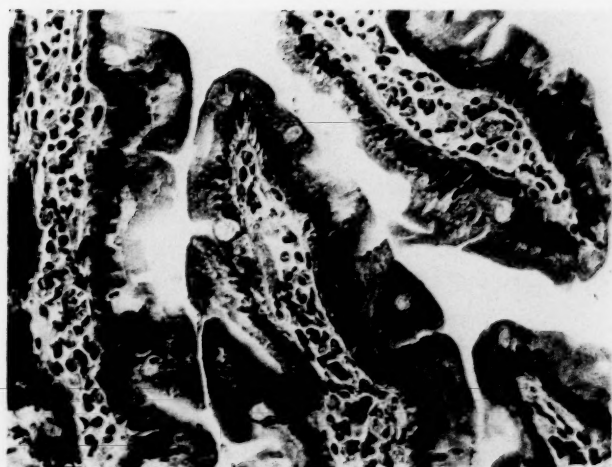


FIG. 3. Normal small intestine. Hematoxylin and eosin, original magnification  $\times 240$ .

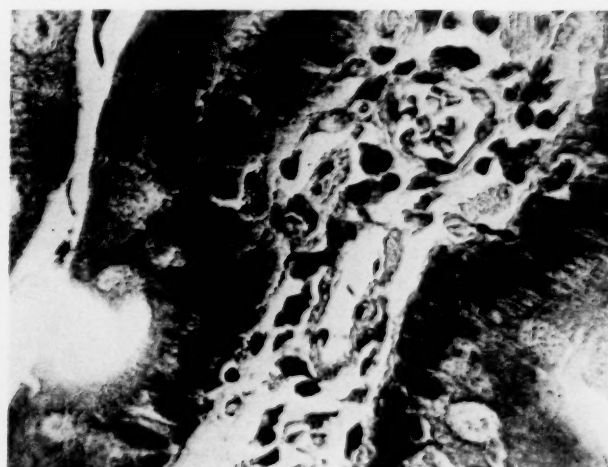


FIG. 4. Normal small intestine. Hematoxylin and eosin, original magnification  $\times 620$ .

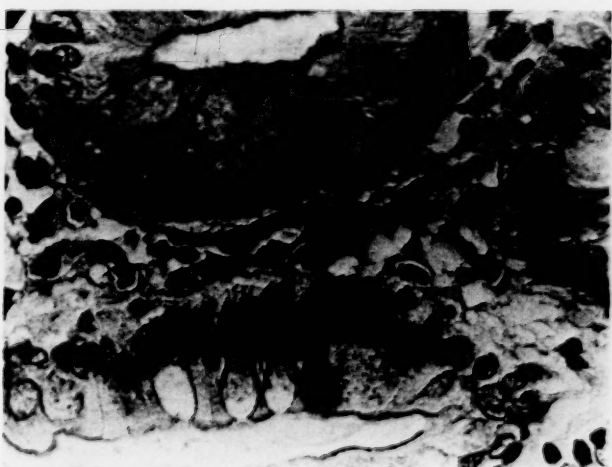


FIG. 5. Small intestine. Hematoxylin and eosin, original magnification  $\times 110$ . Regional enteritis, clinically inactive.

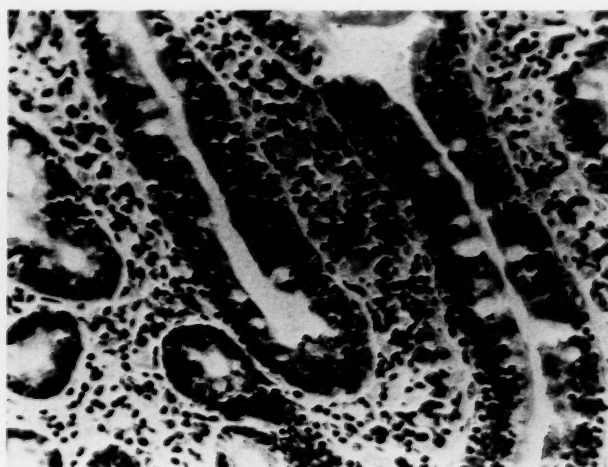


FIG. 6. Small intestine. Hematoxylin and eosin. Typhoid fever, twenty days after onset of symptoms, four days following institution of therapy with chloramphenicol.

intestinal villi cover 1 square mm. of human small intestine, several hundred such villi are available for study. Depending upon the position of the capsule within the small intestine, the specimen will include portions of valvulae conniventes or will consist of strips of mucosa. While gastric specimens obtained with the Wood instrument in our hands regularly include muscularis mucosa, this occurs only infrequently with the Crosby capsule. We assume that the healing of the mucosal defect caused by the biopsy instrument takes place in a fashion similar to that known to occur in the stomach, e.g., the muscularis mucosa contracts at the biopsy site and closes the defect while healing takes place from the adjacent mucosa. As intestinal epithelium is one of the most rapidly regenerating tissues in the body, ultimate covering of the

defect should take place within a matter of days. Infection, hemorrhage or perforation has not been observed in our patients, even in the single case in which an addition to the full thickness of the muscularis mucosa, a deep cut of the submucosa was obtained.

The specimen obtained by the biopsy instrument should be oriented on a piece of filter paper prior to immersion in fixing solution. This will prevent curling of the tissues and will result in a better preparation. In our initial studies we employed neutral buffered 10 per cent formalin solution as our only fixative. Routine hematoxylin and eosin, reticulum and PAS stains were performed on paraffin-embedded material, while special stains for fat were made on frozen sections of gelatin-embedded tissues. Attempts to divide

the specimen while still fresh in order to use additional technics usually resulted in poor preparations. If due precautions are observed, the histological section obtained will be excellent and will show no postmortem changes when the preparation is studied under light microscopy. The finest details of the mucosa can be discerned. The slight suction applied just before the cutting of the specimen causes the capillary network and the tissue spaces in the lamina propria of the intestinal villi to be slightly distended. This separation of cells and structures is of great advantage, for it permits a more detailed analysis of the basement membrane, the reticular framework and cells, and the various channels. Although there are certain differences in the finer architecture of the intestinal mucosa from the duodenum, the jejunum, and the upper and lower ileum, the normal villus will always be rather slender, and the lamina propria when examined under standard conditions in the preprandial state will contain only a small number of cells.

We have been impressed by the uniformity of these findings in our normal control subjects. However, a much greater experience is needed to define the limits of normal and to elucidate the significance of borderline changes. In contradistinction, in cases of enteritis and in atrophy of the mucosa associated with a malabsorption syndrome, definite changes from the normal have been noted. There is blunting and fusion of the villi, variation in the size of the villi, and an increase in the cellularity of the lamina propria. These changes affect the individual villi to varying degrees, but the summation of the

findings in many villi permits a diagnosis. Systemic diseases affecting the intestinal tract diffusely involve individual intestinal villi.

On the basis of our present experience we are quite confident that the amount of tissue removed by the Crosby capsule is adequate for detailed histological analysis, that it will give reproducible results, and will permit clinical-anatomical correlations in all such conditions.

#### SUMMARY

1. An intestinal biopsy capsule triggered by suction and capable of reaching any portion of the gastrointestinal tract has been employed in sixty-three attempts to obtain biopsy specimens from thirty-eight patients. There were twenty-two failures, but the incidence of failure decreased with increasing experience in use of the instrument.
2. The specimen is a 7 mm. disk of mucosa which, if properly processed, yields histological preparations free of traumatic or postmortem changes, and qualitatively superior to previously available material.
3. Illustrative photomicrographs are included.

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# Uropepsin and 17-Hydroxycorticoid Excretion in Normal Subjects and Patients with Peptic Ulcer during Both States of Activity and Quiescence\*

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IN recent years, the determination of urinary uropepsin has been used extensively in the study of gastric secretions both in normal subjects and in patients with gastroduodenal disease [1-6]. Studies of this urinary enzyme have clinical importance as well as relevance in investigations concerning peptic ulcer disease. Evidence that excretion of uropepsin may possibly reflect the intensity of adrenocortical activity [7,8], the known relationship of stress to peptic ulcer, and the reported incidence of peptic ulcer disease in patients receiving adrenal hormone therapy [9,10], has led to much discussion and debate concerning the role of the adrenal cortex in idiopathic peptic ulcer.

The utility of uropepsin determination in these problems is predicated upon the assumption that it reflects gastric secretory activity. It has been reported that uropepsin excretion is elevated in duodenal ulcer disease, normal or somewhat below normal in benign gastric ulcer, and low in cancer of the stomach and pernicious anemia [7]. This is quite similar to the findings of gastric acidity in these conditions and therefore has given credence to the possible usefulness of the test. However, recent evidence has indicated that the level of uropepsin is not necessarily related to gastric secretion of pepsin [8,11,12].

There has also been evidence that uropepsin excretion parallels adrenocortical activity, low values being noted in Addison's disease and above normal values in Cushing's syndrome and following prolonged administration of ACTH or

adrenocortical steroid [7,8]. These observations coupled with the aforementioned clinical phenomena relevant to peptic ulceration and adrenal hormone effects, suggest a possible relationship of idiopathic peptic ulcer to adrenal activity.

It has seemed rational therefore to speculate that in man stress induces excessive adrenocortical activity with resultant hypersecretion of gastric pepsin and acid, and this in turn facilitates ulceration. Consistent with this has been a recent report of an abnormal elevation in plasma 17-hydroxycorticosteroid levels in patients with peptic ulcer [13]. It has been suggested that perhaps these patients are unusually sensitive to adrenocortical hormones, and therefore to stress.

In order that these various facts and observations are not prematurely pieced together to constitute an important theory concerning peptic ulceration in man, the answers to certain important questions must be ascertained. These are: (1) Do patients with active peptic ulcer show an elevated level of uropepsin? (2) Are uropepsin levels in these patients related to activity of the ulcer? (3) Do these patients manifest evidence of adrenal hyperactivity as measured by urinary excretion of 17 OH-steroids? (4) Is the level of 17 OH-steroids related to ulcer activity? (5) Is there a relationship between uropepsin and 17 OH-steroid excretion?

The present study was undertaken to assist in answering these questions, and thereby possibly to shed light on the adrenal-gastric "axis" and its role in peptic ulcerations.

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## METHOD AND MATERIALS

Twenty-four-hour urine collections were analyzed for uropepsin according to the method of West et al. [14]. The completeness of collection was checked by urinary creatinine determinations. If the creatinine index, as calculated from the patient's weight, fell outside the normal range, the determination was discarded from the study. In those instances of multiple twenty-four-hour collections from the same patient, the creatinine index was required to check within 15 per cent.

Sixty-nine uropepsin determinations were made in forty-eight patients (thirty men and eighteen women) with peptic ulcer disease from the outpatient department and the pavilions of The New York Hospital. The age range was nineteen to eighty-five years. Twenty-eight patients had active duodenal ulcer, twelve had inactive duodenal ulcer disease, six had active gastric ulcers including two with "steroid ulcer," and two patients had healed gastric ulcers. The control group consisted of twenty-two hospital personnel composed of physicians, medical students and technicians.

The following facts are pertinent to the method employed. Fresh milk from the same source was used daily as the substrate. The uropepsin concentration was derived from the time required for the buffered urine (pH 4.9) to coagulate casein [14]. The twenty-four-hour uropepsin value was determined by comparison with the time required for known amounts of purified pepsin\* to produce the coagulation of casein. Repeated determinations on the same sample revealed a variation of  $\pm 3$  per cent; five random determinations of twenty-four-hour excretion during a ten-day period in the same normal subject revealed a daily variation of  $\pm 8$  per cent. All urines were collected at room temperature, brought to the laboratory in the fresh state, and the determination was made either immediately or after two to four hours of refrigeration at 10 to 12°C. Repeated determinations upon urine collections in the fresh state, after four hours of refrigeration, revealed no significant change in the value of the enzyme. Repeated determinations on urines kept in the refrigerator and freezer for two days revealed a variation of  $\pm 10$  per cent. That the method indeed determined peptic activity in the urine was shown by the failure to alter enzyme concentration by prior exposure of the urine enzyme to a pH of 1.5 for several hours and by its inactivation on exposure to pH of 10 for several hours. This behavior would appear to exclude catheptic activity as a possible source of error [7]. No significant activity was found in the urine of six patients who had undergone total gastrectomy.

For twenty-four hours prior to the collection of the urine and during the collection, the patient was in-

structed not to take any sedative drug or anticholinergic agent. All urine collections were made on Sunday, the last specimens being voided upon arising Monday morning. Immediately thereafter the patient or subject brought the urine to the gastrointestinal laboratory for determinations.

An aliquot was also taken and frozen for later determination of 17 OH-steroids in forty-eight patients with active and inactive peptic ulcer disease. A modification of the method of Silber and Porter [15] was employed. In such instances, simultaneous determinations of uropepsin and 17 OH-steroids were performed on the same urine specimen. In addition, simultaneous determinations were made in patients with Cushing's disease and after intravenous administration of 40 units of ACTH over an eight-hour period.

## RESULTS

Results of the uropepsin and 17 OH-steroid determinations are shown in Table 1 where values for the normal group are compared to those in the various disease categories and after ACTH administration. Figure 1 demonstrates the distribution of uropepsin levels found in the various conditions. The mean excretion of uropepsin for twenty-four hours in twenty-two normal subjects was 0.62 mg. (range: 0.1 mg. to 1.7 mg.). The mean excretion of uropepsin in twenty-eight subjects with active duodenal ulcer, on the other hand, was 0.92 mg. per twenty-four hours (range: 0.20 mg. to 2.0 mg.). Twelve patients with inactive duodenal ulcer had a mean excretion of 1.11 mg. per twenty-four hours (range: 0.2 mg. to 2.2 mg. per twenty-four hours). The mean excretion in gastric ulcer patients was 1.12 mg. per twenty-four hours (range: 0.64 to 1.9 mg. per twenty-four hours). Although the mean excretion for the patients with active and inactive duodenal ulcer are both higher than normal, the difference between values for normal subjects and patients with active duodenal ulcer is not significant at the 5 per cent level ( $P = 0.08$ ). Differences between the mean values of normal subjects and patients with inactive duodenal and gastric ulcer are significant ( $P = 0.03$  and  $0.02$ , respectively). However, the difficulty of utilizing individual determinations for clinical purposes is indicated by the large spread of the data shown.

Figure 2 shows the values for uropepsin and 17 OH-steroid excretion during periods of activity and inactivity in the same subjects. The value plotted for each subject represents the value obtained during the active period of the ulcer minus that obtained during a period of

\* Pepsin (crystallized), porcine origin, obtained from Armour and Co., Chicago, Illinois.

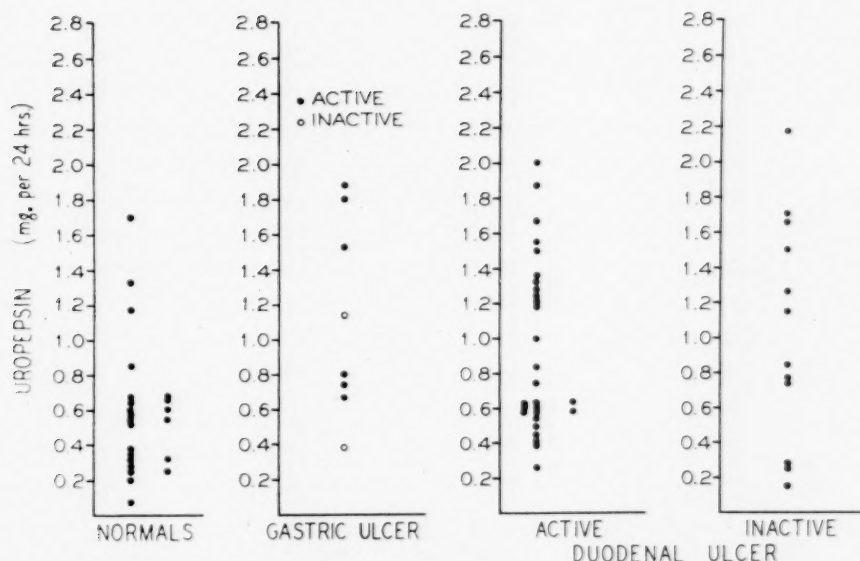


FIG. 1. Distribution of values for twenty-four-hour uropepsin excretion in normal subjects and in patients with active and inactive peptic ulcers.

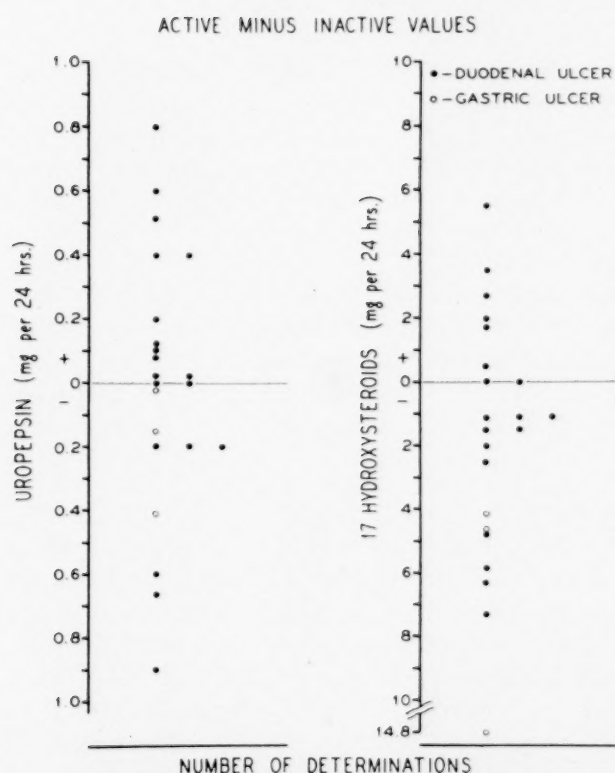


FIG. 2. Relationship of uropepsin and 17-hydroxysteroid determinations during periods of ulcer activity and inactivity. Each value plotted represents a determination during a period of activity minus one made during a period of inactivity for a single patient.

inactivity. The distribution of the values shows the absence of a consistent elevation of uropepsin or 17 OH-steroid during periods of activity as compared to inactivity.

SEPTEMBER, 1958

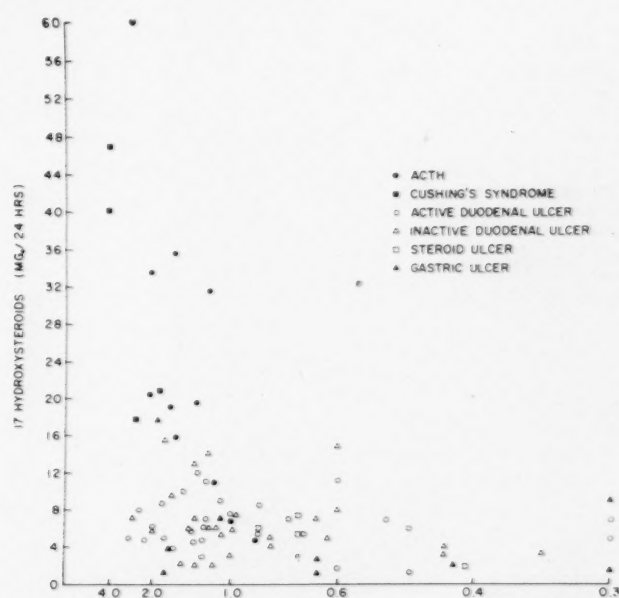


FIG. 3. Relationship of uropepsin and 17-hydroxysteroid values obtained simultaneously under various conditions. Abscissa represents uropepsin (mg./24 hours.)

Figure 3 compares the level of uropepsin and 17 OH-steroids present simultaneously in the various conditions. The distribution of the values in Figure 3, together with the data shown in Table I, indicate that whereas the 17 OH-steroids were not significantly elevated in patients with active or inactive ulcer disease, they were elevated in patients with Cushing's syndrome and after ACTH administration. In addition, in patients with Cushing's syndrome and after ACTH administration, elevated 17 OH-steroid

TABLE I

Data	Determination of Uropepsin				Determination of 17 OH-Steroids		
	Mean Excretion (mg./24 hr.)	Range (mg./24 hr.)	$\pm 2$ SD*	P Value	Mean Excretion (mg./24 hr.)	Range (mg./24 hr.)	$\pm 2$ SD*
Normal subjects . . . . .	0.62	0.1 -1.7	0.83	.....	6.6	2-12	7.4
Active duodenal ulcer . . . . .	0.92	0.2 -2.0	1.22	0.08	9.65	2-12	8.4
Inactive duodenal ulcer . . . . .	1.11	0.2 -2.2	1.40	0.03	6.62	2-16	7.4
Gastric ulcer . . . . .	1.12	0.6 -1.9	1.13	0.02	5.4	1-18	10.6
Administration of ACTH . . . . .	1.61	0.9 -3.0	1.23	<0.01	23.8	5-60	30.0
Cushing's syndrome . . . . .	3.2	1.9 -4.0	1.74	<0.01	31.5	18-47	24.6

\*SD = Standard deviation.

levels were accompanied by elevated uropepsin levels. It is also of interest that several patients with gastric ulcer incident to adrenocortical steroid therapy for rheumatoid arthritis had no elevation of either 17 OH-steroid or uropepsin excretion, at a time when the ulcer persisted and the hormone had been discontinued.

## COMMENTS

In determining the accuracy of the method used for uropepsin determination, the reliability of the twenty-four-hour urine collection is of utmost importance. Many clinical studies of this urinary enzyme have been based on determinations in specimens collected over a period of only a few hours, with insufficient information as to the conditions of collection or of the experimental error. Under the conditions used in these determinations, a variation of  $\pm 3$  per cent was found for repeated measurements on the same urine specimen, and the method used was shown to be specific for the determination of uropepsin activity.

The demonstration of increased uropepsin in patients with Cushing's disease, and after ACTH administration, is in agreement with findings previously noted [7,8]. However, it does not follow that an increased level of uropepsin reflects a similar change in gastric secretion. Recent evidence has indicated that the excretion of uropepsin may not correlate well with gastric secretion of pepsin [8,11,12]. In this connection

the experiments of Woodward et al. are pertinent [16]. They found that after vagotomy, secretion of gastric juice and acid is markedly decreased while uropepsin excretion remains unchanged. Secondly, while there is a correlation between the hourly secretion of hydrochloric acid and pepsin, there is no such relationship between output of uropepsin and the production of either hydrochloric acid or gastric pepsin. In the instance of ACTH stimulation, it has been pointed out that excretion of uropepsin is proportionately higher than the level in the stomach, and this in effect has been attributed to change in the renal clearance of pepsinogen [17].

It is still questionable whether administration of adrenal corticosteroids or ACTH increases the output of gastric acid and/or pepsin significantly except over prolonged periods (circa twenty-one days or more). In such long term experiments in man, an increase in acid and uropepsin excretion with ACTH and prednisone has been demonstrated [17]. In similar experiments of shorter duration, however, there has been no demonstration of changes of pepsin secretion measured in stomach, blood or urine, after ACTH and compounds E and F [11,17].

The question of the role of the adrenal gland in idiopathic duodenal ulceration is, of course, pertinent to this problem. Studies have shown variously that in patients with peptic ulcer, the response of the adrenal cortex to stimulation is subnormal, normal, or high [13,18,19]. Our

own work indicates that there is normal activity of the adrenal cortex, as measured by 17-OH-steroid excretion, in patients with duodenal ulcer and that there is no difference in excretion between the activity and quiescent states.

There appears to us to be no evidence that the patient with idiopathic duodenal ulcer has abnormal adrenocortical activity as determined by the urinary 17-hydroxycorticoid excretion. Moreover, no difference is apparent in uropepsin excretion between the active and inactive states of the disease. The effect of stress in the pathogenesis of duodenal ulcer may not be mediated entirely via increase in the acid peptic mechanism. In this regard the reports of Hirschowitz et al. (8,17) of steroid ulcers occurring in subjects after a few days of either ACTH or compound F, at a time when there was no significant change in the level of gastric acid or pepsin or blood pepsin, would appear to be pertinent. As implied in these studies, changes which occur in the viscosity of the gastric secretion as a result of adrenocortical activity warrant further study.

#### SUMMARY

Twenty-four-hour uropepsin determinations were made in normal subjects, and patients with gastric ulcer, active and inactive duodenal ulcer, and steroid ulcers; in all, ninety-one determinations in seventy subjects. In addition, the twenty-four-hour urinary excretion of 17-hydroxycorticoids was determined in forty-eight of the patients.

Significant differences were found in the uropepsin excretion in the groups of patients with gastric ulcer and inactive duodenal ulcer when compared to the normal group. However, the standard deviation of the results within the groups was so large that any attempt at delineation of normal and abnormal ranges would be of minimal value. There was no significant difference between uropepsin values in patients with active duodenal ulcer and in normal subjects. In addition, there was no significant difference between uropepsin values in patients with duodenal ulcer during periods of activity of their disease and intervals of well-being.

The 17-hydroxycorticoid excretion remained within normal limits in patients with active and inactive ulcer, and in those in whom steroid ulcers had developed. A positive correlation of uropepsin and 17-hydroxycorticoids was obtained only in a small group of patients either with Cushing's syndrome or under treatment

with ACTH; i.e., uropepsin values were consistently elevated when there was increased 17-hydroxycorticoid output.

This study demonstrated: (1) either that urinary uropepsin does not accurately reflect gastric secretory activity or that the intensity of gastric secretory activity bears no relationship to activation of duodenal ulcer; (2) that there is no evidence for increased adrenocortical activity in patients with idiopathic duodenal ulcer, particularly during periods of activation; and (3) that when adrenocortical hyperactivity, as reflected by urinary 17-hydroxycorticoid excretion does exist, urinary uropepsin is predictably elevated.

*Acknowledgment:* The authors wish to acknowledge the technical help of Mrs. Doris Simon and Mrs. Gloria Van Duyn and the valuable laboratory aid and advice given us by Dr. Melvin Horwith.

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# Zoxazolamine\*

## *Physiological Disposition, Uricosuric Properties*

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ZOXAZOLAMINE (2-amino-5-chlorobenzoxazole)‡ in divided daily dosage of 0.75 to 3.0 gm. has been widely employed for the past two years in the relief of skeletal muscle spasm. Unlike curare, decamethonium and succinylcholine, which act peripherally, the action of zoxazolamine appears to be central, depressing transmission through subcortical, brain stem and spinal polysynaptic pathways by an as yet obscure mechanism.

In this communication are recorded data, previously summarized elsewhere [1], on the physiological disposition of zoxazolamine in man. In the course of these studies it was noted that in addition to its muscle relaxant action the drug also has a marked uricosuric effect, as will herein be described. Reed et al. [2] have independently observed this uricosuric action of the drug, reporting a fall in serum urate from 10.5 to 3.7 mg. per cent in a gouty subject receiving a daily dose of 0.75 gm. In a second gouty subject, taking the same dosage, a threefold increase in  $C_{urate}/C_{creatinine}$ , with corresponding increase in urinary urate excretion and fall in serum urate, was observed.

### METHODS

*Estimation of Zoxazolamine.* Zoxazolamine was isolated from alkalinized biological materials by extraction into ethylene dichloride. The drug was then extracted from ethylene dichloride solution into hydrochloric acid and measured spectrophotometrically at 278 m $\mu$ . where it exhibits a pronounced peak.

*Procedure for Plasma and Urine.* To 3 ml. of plasma or urine in a 60 ml. glass-stoppered bottle was added

‡ Available as Flexin, McNeil Laboratories, Inc., Philadelphia, Pa.

\* From the Laboratory of Chemical Pharmacology, National Heart Institute, National Institutes of Health, U. S. Public Health Service, Department of Health, Education and Welfare, Bethesda, Md.; the Departments of Medicine, The Mount Sinai Hospital, and Columbia University College of Physicians and Surgeons; and the Research Service, Third (New York University) Medical Division, Goldwater Memorial Hospital, New York, N. Y. This work was supported in part by a grant-in-aid (A-162) from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, and a grant from the Arthritis and Rheumatism Foundation, New York State Chapter.

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1 ml. of 0.5 N NaOH and 30 ml. of ethylene dichloride previously purified by successive washings with 1N HCl, 1N NaOH and water. The bottle was shaken for sixty minutes and the contents transferred to a test tube and centrifuged. The supernatant aqueous layer was removed by aspiration with a fine tipped pipette. Twenty ml. of the ethylene dichloride phase was transferred to a 60 ml. glass-stoppered bottle containing 3 ml. of 1N HCl. The bottle was shaken for five minutes and the contents transferred to a test tube and centrifuged. About 1.5 ml. of the supernatant aqueous phase was transferred to a quartz cuvet† and the optical density determined at 278 m $\mu$ . in an ultraviolet spectrophotometer (Beckman).

*Procedure for Tissues.* Five gm. of tissue was homogenized with 10 ml. of water in an electrically driven homogenizer. Three ml. of the homogenate was transferred to a 60 ml. glass-stoppered bottle. The subsequent procedure was the same as described for the estimation of zoxazolamine in plasma and urine.

A reagent blank employed throughout the procedure gave an optical density of not more than 0.015 when 1N HCl was used for the zero setting. Standards were prepared by taking 2 ml. of suitably diluted standard solutions§ and adding 8 ml. of 1N HCl. The optical densities were found to be proportional to the concentration of the standards. Zoxazolamine added to the biological material in amounts from 20 to 100  $\mu$ g. was recovered with adequate precision ( $95 \pm 3$  per cent).

*Estimation of Uricosuric Activity.* The uricosuric properties of zoxazolamine were studied in thirty-two experiments, described in the text, on twenty-nine

† The cuvetts were obtained from Pyrocell Manufacturing Co., 207 East 84th Street, New York 28, New York. The outside dimensions of the cuvetts were 10 by 10 by 50 mm., and their capacity was 1.5 cc.

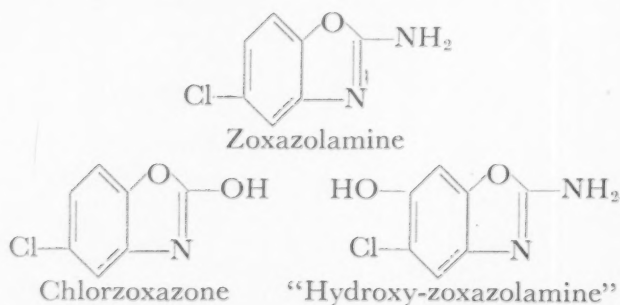
§ A standard solution was prepared by dissolving 50 mg. of zoxazolamine in 2 ml. of 0.5 N hydrochloric acid and diluting to 1 L. with water.

gouty subject's all in the intercritical phase of the disorder. These experiments included sixteen renal clearance studies in which  $C_{urate}$ ,  $C_{inulin}$  and  $C_{PAH}$  were measured concurrently, using standard techniques as previously described [3]. After three fifteen-minute control periods, the drug was given orally in dosages indicated in the text. Postmedication urine collections were made by indwelling catheter at twenty-minute intervals for two to three hours. In additional experiments pyrazinamide, probenecid, salicylate, a sulfoxide analogue of phenylbutazone (G-28315) or sodium bicarbonate was administered one hour before or after ingestion of zoxazolamine in order to determine their effect on zoxazolamine uricosuria.

Inulin, para-aminohippurate and urate were determined by the standard methods described elsewhere [3,4].

### RESULTS

*Physiological Disposition of Zoxazolamine. Metabolism of zoxazolamine in man:* Four normal human subjects each received 1.0 gm. of zoxazolamine in a single oral dose, and the urine was collected over a twenty-four-hour period. Less than 1.0 per cent of the dose of zoxazolamine was recovered unchanged in these urine samples, indicating the essentially complete biotransformation of the drug. Isolation studies [1] showed that about 2 per cent of the administered dose of the drug was excreted as a metabolite in which the amino group was replaced by a hydroxyl group (chlorzoxazone) and about 50 per cent as the glucuronide of a metabolite formed by the introduction of a hydroxyl group into the benzene ring ("hydroxy-zoxazolamine").



In the course of these isolation studies a crystalline compound was recovered from the urine in relatively large amounts. At first thought to be another metabolic product of the drug, the compound proved to be uric acid. It was this accidental observation which gave us the first clue to the potent uricosuric properties of zoxazolamine.

*Plasma drug levels after oral administration of*

*zoxazolamine to human subjects:* Six normal subjects each received a single oral dose of 0.75 gm. to 1.0 gm. of zoxazolamine, and the plasma levels of the drug were measured at various time intervals. The absorption of the drug was fairly rapid; peak plasma levels, ranging from 3.0 to 12.0 mg./L., were obtained between the first and third hour after administration of the dose. By the seventh hour the plasma levels had fallen to a low value (less than 0.4 mg./L.), indicating relatively rapid metabolism of the drug in man. In Figure 1 are given representative plasma levels obtained in three patients who received a single 1 gm. oral dose of the drug.

Five other subjects received 1.5 gm. of the drug in three divided doses each day for three days. The plasma levels of the drug obtained three hours after the last dose were essentially the same as those obtained after the initial dose of the drug, thus indicating no accumulation of the drug.

*Plasma drug levels after oral and intravenous administration of zoxazolamine to dogs:* Two dogs each received 200 mg./kg. of zoxazolamine orally and the plasma levels of the drug were measured at various time intervals. Two weeks later the same animals were given 30 mg./kg. of the drug intravenously and the plasma concentrations of the drug were again determined. Representative data in one of these dogs are presented in Figure 2. Following intravenous administration plasma levels of the drug disappeared at a fairly rapid rate, with a half-life of about forty minutes. The absorption of the drug was rapid after oral administration as indicated by the occurrence of a peak plasma level between the second and third hour after administration of the dose. The concentration of the drug in plasma fell off at a considerably slower rate after oral administration than after intravenous injection, presumably due to sustained absorption of the drug from the gastrointestinal tract.

*Distribution of zoxazolamine in tissues:* The distribution of zoxazolamine was examined in the tissues of three dogs which were sacrificed at various times after intravenous injection of the drug. (Table 1.) The concentrations of the drug in the various tissues obtained one hour after the dose were, in general, two to four times its concentration in plasma. At four hours virtually no drug was detected in the various tissues, which is in accord with its rapid rate of biotransformation.

*Uricosuric effect of zoxazolamine.* The initial studies were designed to determine the time of onset and duration of uricosuric effect in gouty subjects after administration of a single oral dose of zoxazolamine, by measuring the post-

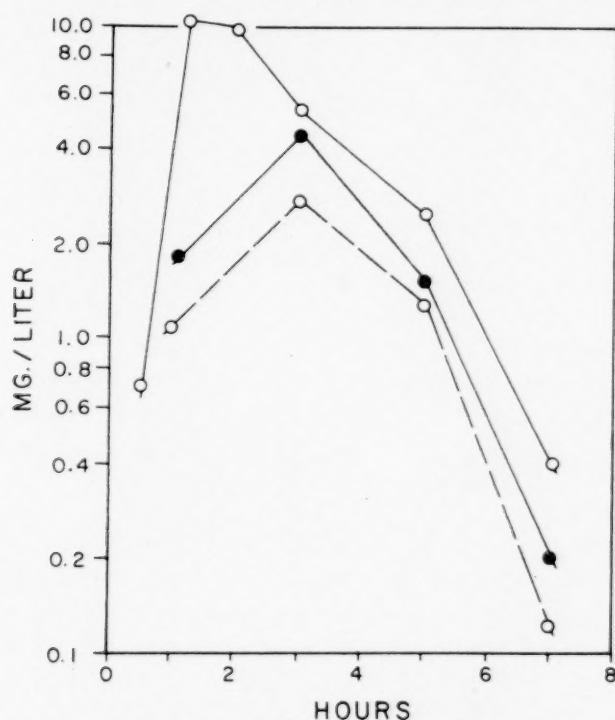


FIG. 1. Plasma levels of zoxazolamine after administration of single 1.0 gm. oral doses of the drug to three human subjects.

medication urinary urate excretion in two-hourly voidings. The urinary urate excretion after a 1.0 gm. dose increased and reached a fivefold peak within two hours after administration of the drug and was demonstrable for four to six hours thereafter; this time course is in accord with the data on rate of absorption from the gastrointestinal tract. A similar approximately fivefold uricosuric response, with associated decline in serum urate levels, could be demonstrated with 0.25 gm. doses, and indeed with as little as 50 mg. (Table II.) At these low dosage levels the over-all twenty-four-hour excretion of urinary urate increased 40 to 65 per cent.

When administered daily to gouty subjects zoxazolamine produces a marked and continued uricosuric response. For example, 1 gm. given daily in four divided doses caused a pronounced and sustained fall in serum urate; in patient M. F. from 12.1 to 5.6 mg. per cent by the third day, in L. W. from 9.1 to 3.9 mg. per cent by the third day. This was associated with a maximum

rise in urinary urate excretion from 375 to 680 mg./twenty-four hours and from 382 to 865 mg./twenty-four hours respectively. As with other uricosuric agents, the increase in urinary urate output then tended to fall off somewhat,

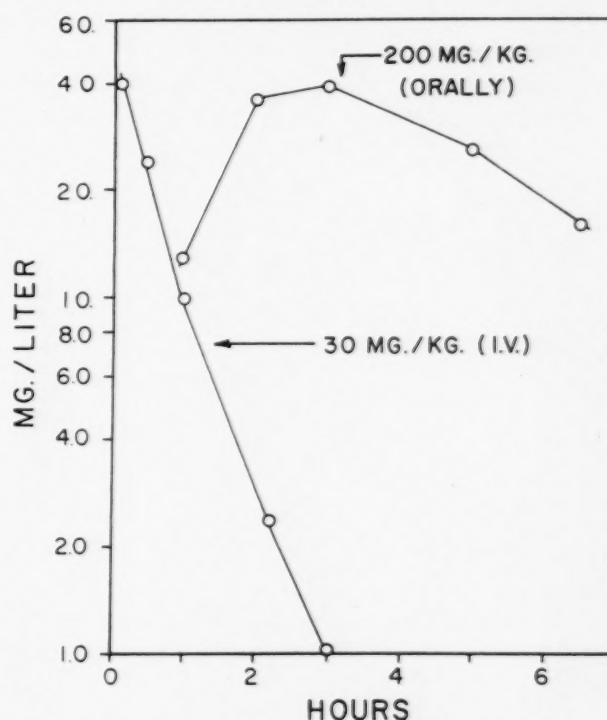


FIG. 2. Plasma levels of zoxazolamine after oral and intravenous administration to the dog.

with sustained lowering of the serum urate as long as the drug was administered.

One-half gram daily, given in divided doses, caused a fall in serum urate; in patient T. M.,

TABLE I  
DISTRIBUTION OF ZOXAZOLAMINE IN VARIOUS TISSUES IN THREE DOGS

Time (hr.) . . . . .	1	1	4
Dose (mg./kg.)* . . . . .	60	30	30
Plasma . . . . .	22	10	1.0
Muscle . . . . .	27	17	<3.0
Kidney . . . . .	44	20	<3.0
Liver . . . . .	56	29	<3.0
Brain . . . . .	76	35	<3.0
Fat . . . . .	89	43	<3.0

\* The drug was administered by intravenous injection over a five-minute period.

from 10.5 to 7.4 mg. per cent, in M. W. from 10.1 to 9.7 mg. per cent, in S. H. from 10.1 to 7.0 mg. per cent with a rise in urinary urate excretion from 580 to 705 mg./twenty-four

hours, 819 to 930 mg./twenty-four hours and 447 to 523 mg./twenty-four hours, respectively. Patient A. R. received 0.25 gm. as a single daily dose; the serum urate fell from 9.4 to 6.2 mg. per cent, the urinary urate excretion at the end of one week was 702 mg./twenty-four hours as com-

TABLE II  
TIME OF ONSET AND DURATION OF EFFECT OF SINGLE, ORAL  
DOSE OF ZOXAZOLAMINE ON SERUM AND URINARY URATE  
IN TWO GOUTY SUBJECTS

Patient	Time (hr.)	Urate		
		Serum (mg. %)	Urine	
			(mg./hr.)	(mg./24 hr.)
O. G.	Premedi- cation	10.2	20-32	530
<i>Zoxazolamine, 0.25 gm. oral dose</i>				
	0- 2	.....	81	...
	2- 4	7.6	80	...
	4- 6	.....	34	...
	6-24	7.4*	18	740
A. R.	Premedi- cation	8.9	23	550
<i>Zoxazolamine, 0.05 gm. oral dose</i>				
	0- 2	.....	102	...
	2- 4	.....	90	...
	4- 6	6.7	47	...
	6-24	9.4*	24	909

\* Serum urate levels at the end of twenty-four hours.

pared with a premedication output of 550 mg./twenty-four hours. It should be pointed out that because of the relatively rapid metabolism of the drug and the variable interval between the last dosage of drug and the time of serum urate determination, the values cited do not, in many cases, reflect the maximal response to the drug.

In five experiments in which the uricosuric potency of zoxazolamine was compared with that of probenecid, it was found that 0.5 gm. daily of zoxazolamine, administered in two divided doses, was about equal to or greater than 1.0 to 1.5 gm. of probenecid. A pronounced uricosuric effect ordinarily was obtained with much smaller doses of zoxazolamine than required for probenecid.

In one instance, patient R. K., a satisfactory uricosuric response could not be obtained with

zoxazolamine even in doses of 1.0 gm./day in divided dosage. This patient also did not respond to the administration of probenecid in doses as high as 4 gm./day or to G-28315 [5] in doses of 800 mg./day.

*Renal Clearance Studies.*  $C_{urate}$ ,  $C_{inulin}$  and  $C_{PAH}$  were determined before and after administration of a single oral dose of zoxazolamine: in one experiment with 1.0 gm. dosage, in two with 0.5 gm.; in seven with 0.25 gm.; in three with 0.1 gm. A similar pattern of response was obtained throughout this dosage range, as indicated in the representative experiments summarized in Table III.  $C_{urate}/C_{inulin}$  did not change in the first postmedication twenty-minute urine collection, except in one instance in which a two and a half fold rise occurred in a ten to twenty minute collection period; generally there was a two and a half to threefold increase in  $C_{urate}/C_{inulin}$  in the twenty to forty minute period; a four and a half to ninefold (usually a five to sixfold) peak increase in  $C_{urate}/C_{inulin}$  occurred almost invariably in the forty to sixty minute period; and thereafter there was a continued marked increase in  $C_{urate}/C_{inulin}$ , sometimes slowly falling off, until the end of the two to three hours of urine collection. In association with the increased urinary urate excretion there was an invariable fall in plasma urate, averaging approximately 1.0 mg. per cent at the termination of the clearance studies.

$C_{inulin}$  was unaffected in some experiments, fell slightly or moderately in others. (Table III.)  $C_{PAH}$  did not change appreciably except for a sustained decrease (mean 18 per cent) after 1.0 gm. dosage.

Having thus found that as little as 0.1 gm. of zoxazolamine usually elicits what appears to be the maximal increase in urate clearance obtainable with the drug, smaller doses were then employed to estimate the lowest effective dosage. A uricosuric effect could be detected with the administration of as little as 15 mg. of the drug, which caused a peak 80 per cent increase in  $C_{urate}/C_{inulin}$ . (Table III.)

*Effect of Pyrazinamide, Salicylate, Probenecid, G-28315 and Bicarbonate on Zoxazolamine Uri-  
cosuria.* Pyrazinamide, which causes a marked decrease in  $C_{urate}$  [6], was found to counteract the uricosuric action of zoxazolamine. This is illustrated in two experiments summarized in Table IV. In patient I. M. a sharp increase in  $C_{urate}/C_{inulin}$  produced by zoxazolamine steadily declined after administration of pyrazinamide to

TABLE III  
RESULTS OF REPRESENTATIVE EXPERIMENTS EMPLOYING RENAL CLEARANCE TECHNIQS  
(VALUES NOT CORRECTED TO STANDARD SURFACE AREA)

Patient, Age (yr.), B.S.A.	Period (min.)	Purate (mg. %)	Curate (ml./min.)	Cinulin (ml./min.)	Curate/Cinulin (%)	C <sub>PAH</sub> (ml./min.)
C. R., 67, 1.86 M <sup>2</sup>	-45 to 0	9.7	5.1	91.8	5.4	341
	<i>Zoxazolamine 0.5 gm. orally</i>					
	0-19	9.7	5.0	82.5	6.1	316
	19-38	....	19.2	89.0	21.6	316
	38-58	....	25.5	91.0	28.0	319
	58-98	9.4	26.4	84.1	31.4	311
	98-143	8.6	25.6	92.1	27.8	310
M. C., 59, 2.01 M <sup>2</sup>	-45 to 0	10.1	7.1	56.4	12.6	297
	<i>Zoxazolamine 0.25 gm. orally</i>					
	0-21	9.6	7.6	58.5	13.0	349
	21-40	....	19.5	56.0	34.8	365
	40-50	....	27.0	62.2	43.4	335
	50-90	9.3	31.6	57.7	54.8	334
	90-122	8.8	29.2	62.9	46.4	328
M. W., 57, 1.91 M <sup>2</sup>	-45 to 0	9.6	8.6	106	8.1	417
	<i>Zoxazolamine 0.1 gm. orally</i>					
	0-17	9.6	6.9	85.0	8.1	342
	17-37	....	19.0	97.8	19.4	404
	37-57	....	40.3	99.8	40.4	493
	57-97	9.1	60.9	92.6	65.8	403
	97-137	9.0	55.1	88.7	62.1	375
F. W., 54, 1.95 M <sup>2</sup>	-45 to 0	6.2	9.9	126	7.9	495
	<i>Zoxazolamine 0.05 gm. orally</i>					
	0-21	6.2	9.9	107	9.3	447
	21-40	....	23.0	99	23.2	428
	40-81	6.2	33.2	105	31.6	430
	81-120	....	33.0	114	28.9	484
	120-160	6.2	20.6	100	20.6	450
M. R., 51, 1.98 M <sup>2</sup>	-45 to 0	7.2	7.3	121	6.0	436
	<i>Zoxazolamine 0.015 gm. orally</i>					
	0-20	7.0	8.3	115	7.2	492
	20-40	....	9.9	94	10.5	424
	40-80	7.0	12.2	113	10.8	441
	80-120	7.4	7.1	91	7.8	395

a value somewhat below the premedication figure. In L. O. the prior administration of pyrazinamide effectively nullified any significant uricosuric response to the administration of 0.25 gm. zoxazolamine.

Salicylate, which also causes urate retention when administered in ordinary analgesic dosages [7], counteracts zoxazolamine uricosuria, as indicated in three clearance experiments. In the experiment summarized in Table IV,  $C_{urate}/C_{inulin}$  rose from 6.9 to 41.6 per cent in response to a 0.25 gm. dose of zoxazolamine, then fell more rapidly than would be anticipated from other clearance studies (Table II) when

sodium salicylate was slowly infused (11 mg./minute, plasma salicylate level <10 mg. per cent). In the later periods the rate of salicylate infusion was increased to 25 mg./minute and then to 44 mg./minute (plasma salicylate levels >20 mg. per cent); the urate clearance began to rise again, presumably due to the uricosuric action of salicylate in large dosage. The inhibitory effect of salicylate on zoxazolamine uricosuria was demonstrated also when both drugs were given together orally. In patient O. G., the serum urate was reduced from 10.3 to 6.6 mg. per cent by the administration of 0.75 gm. zoxazolamine daily in divided doses. When

TABLE IV  
RENAL CLEARANCE STUDIES OF EFFECT OF PYRAZINAMIDE (PZA), SALICYLATE AND PROBENECID  
ON ZOXAZOLAMINE URICOSURIA  
(VALUES NOT CORRECTED TO STANDARD SURFACE AREA)

Patient, Age (yr.), B.S.A.	Period (min.)	Purate (mg. %)	Curate (ml./min.)	Cinulin (ml./min.)	Curate/Cinulin (%)	CPAH (ml./min.)
I. M., 39, 1.76 M <sup>2</sup>	-45 to 0	5.7	10.3	88.6	11.7	491
	<i>Zoxazolamine 0.1 gm. orally</i>					
	0-20	....	12.0	90.0	13.3	535
	20-40	5.2	36.5	87.5	41.8	505
	40-60	....	42.0	73.5	57.5	450
	<i>PZA 1.0 gm. orally</i>					
	60-80	5.2	41.7	79.5	52.5	458
	80-100	....	36.2	72.8	49.8	550
	100-120	5.4	23.5	75.0	31.4	483
	120-140	....	15.0	73.0	20.6	535
	140-180	5.4	6.6	70.6	9.2	517
L. O., 40, 1.87 M <sup>2</sup>	-45 to 0	9.7	6.3	145	4.4	464
	<i>PZA 1.0 gm. orally</i>					
	0-18	....	5.3	133	4.0	423
	18-38	9.2	2.2	126	1.7	427
	38-58	....	1.3	128	1.0	445
	58-78	9.6	1.5	126	1.2	408
	<i>Zoxazolamine 0.25 gm. orally</i>					
	78-108	9.8	1.4	121	1.2	415
	108-138	10.2	6.0	127	4.7	420
	138-179	9.9	8.0	134	6.0	434
I. S., 55, 1.88 M <sup>2</sup>	-45 to 0	10.6	9.3	134	6.9	469
	<i>Zoxazolamine 0.25 gm. orally</i>					
	0-18	....	10.5	139	7.6	495
	18-35	10.6	24.4	128	19.1	607
	35-53	....	45.4	128	35.4	560
	53-65	9.6	61.1	147	41.6	602
	<i>Sodium salicylate 3 gm. in 500 ml. saline solution intravenously</i>					
	65-75	....	41.6	141	35.2	570
	75-88	9.6	28.9	106	27.2	458
	88-110	9.1	26.9	115	23.4	444
	110-125	....	14.3	128	11.2	459
	125-140	8.8	17.2	128	13.4	476
	140-155	....	19.2	143	13.4	489
	155-167	8.8	23.8	145	16.5	520
T. R., 41, 2.17 M <sup>2</sup>	-45 to 0	7.8	9.6	92.0	10.4	602
	<i>Zoxazolamine 0.25 gm. orally</i>					
	0-23	7.5	9.7	92.0	10.5	472
	23-39	....	9.5	89.5	10.6	550
	39-61	....	30.0	87.2	34.4	436
	<i>Probenecid 1.0 gm. intravenously</i>					
	61-80	7.4	62.5	92.0	68.0	523
	80-100	....	59.5	86.5	68.8	550
	100-120	7.2	54.1	92.0	58.9	500

sodium salicylate, 1.8 gm./day in divided dosage, was then added to zoxazolamine, the serum urate level rose to 9.6 mg. per cent. When salicylate was then discontinued but zoxazolamine maintained, the serum urate fell to 6.6 mg. per cent.

Probenecid may have some additive effect, since in one experiment a three and a half fold rise in  $C_{urate}/C_{inulin}$  produced by 0.25 gm. of zoxazolamine in the forty to sixty minute post-medication collection period (when a peak response usually was obtained) promptly doubled after intravenous injection of 1.0 gm. of probenecid. A similar experiment with the uricosuric drug, G-28315, gave comparable results.

Alkalinization of the urine by intravenous injection of sodium bicarbonate had no significant effect on the magnitude of zoxazolamine uricosuria.

*Electrolyte Balance Study.* One gouty subject (O. G.) was maintained on a constant low-sodium diet to which was added 3.0 gm. sodium chloride/day. After several days of equilibration on the prescribed diet, a three-day control period was started. On the fourth day, zoxazolamine, 0.25 gm. three times a day, was administered orally for three days. The study was continued for four more days after the discontinuance of zoxazolamine. Daily urine and blood samples were collected, and measurements of sodium, potassium, chloride, phosphate, uric acid and creatinine were made. During the control period, the mean twenty-four-hour urinary sodium excretion was 45.9 mEq.; potassium, 51.4 mEq., and chloride, 50.7 mEq. With zoxazolamine administration the mean excretion of sodium, potassium and chloride was 48.6, 43.4 and 48.5 mEq./twenty-four hours, respectively. No significant changes were observed during the postmedication period. Serum sodium, potassium and chloride remained unchanged throughout. There were no significant changes in creatinine and phosphate excretion. During the period of zoxazolamine administration the urinary urate excretion increased from a mean of 530 mg./twenty-four hours to a mean of 621 mg./twenty-four hours, the serum urate fell from 10.3 to 6.6 mg. per cent.

*Side Reactions.* In the two patients who received 1 gm. of the drug in a single oral dose, and in one of two who received 1 gm. in four divided doses, dizziness, drowsiness and an unsteady gait developed which persisted for some twelve hours. One subject after taking 0.5 gm.

in two divided doses had similar complaints of lesser degree. No other side reactions were noted.

#### COMMENTS

The results of this study show that zoxazolamine is a potent uricosuric agent. Like other uricosuric agents previously investigated by renal clearance technics [3,5,8,9], zoxazolamine appears to exert its uricosuric action by inhibiting tubular reabsorption of urate. There is no indication that the drug causes an increase in filtered urate load either by enhanced glomerular filtration rate (indeed, this may be reduced) or decreased protein binding of urate. As shown elsewhere [10], the plasma urate is virtually wholly ultrafiltrable in the normal and gouty subject, hence this factor does not enter into considerations of the mechanisms of drug uricosuria.

The finding of potent uricosuric activity in zoxazolamine is of considerable interest since the drug possesses a chemical structure entirely different from that of other known uricosuric agents. Zoxazolamine is a weak base whereas probenecid, the various phenylbutazone analogues, cinchophen and salicylate are all strongly acidic compounds. In fact, it has recently been shown [11] that in the phenylbutazone series uricosuric potency increases with increasing acidity of the molecule.

Zoxazolamine is metabolized in man to a compound in which the amino group is replaced by a hydroxyl group (chlorzoxazone). This metabolite has the muscle relaxant activity of the parent drug and has recently been introduced for this purpose.\* However, chlorzoxazone apparently possesses no uricosuric activity (in 1.0 gm. daily dose no lowering of the serum urate was observed), in oral doses up to 0.25 gm. "Hydroxy-zoxazolamine" also possesses no uricosuric activity.

Physiological disposition studies show that zoxazolamine is rapidly absorbed and that the drug disappears almost completely from the body in about six hours. This finding is in accord with the results showing that its uricosuric activity persists for about six hours after a single oral dose. It is therefore advisable to administer the drug in divided doses throughout the day.

\* Paraflex, McNeil Laboratories, Inc., Philadelphia, Pa.

The uricosuric potency of zoxazolamine in acute clearance experiments is indicated by comparison with other uricosuric agents in respect to the minimum dose required to elicit a pronounced increase in urate clearance. This is of the order of 15 to 50 mg. for zoxazolamine, 35 to 50 mg. for G-28315, 100 to 120 mg. for probenecid, 150 mg. for G-25671, 700 mg. for phenylbutazone and 1,000 mg. for salicylate. It should not be inferred that these renal clearance data necessarily reflect the relative clinical efficacy of zoxazolamine, which must be established by clinical trial.

The experience with zoxazolamine as a muscle relaxant has disclosed a variety of side effects, chiefly nausea, vomiting, anorexia, drowsiness, lightheadedness and headache, with occasional occurrence of drug rash. As indicated in the text, some of these reactions were encountered in the present study but not at the relatively low dosages sufficient to elicit a vigorous uricosuric response in most patients. A muscle relaxant effect is not to be expected at such reduced dosage levels.

#### SUMMARY

Zoxazolamine (2-amino-5-chlorobenzoxazole), a drug currently employed for the relief of muscle spasm, was found to have potent uricosuric properties. A study was made of the physiological disposition of this drug in man and of its effect on the renal excretion of urate in gouty subjects.

Zoxazolamine is fairly rapidly absorbed from the gastrointestinal tract, peak plasma levels being obtained between the first and third hour after oral administration. It soon disappears from the body; seven hours after oral administration of the drug no detectable amounts are present in the blood plasma. Less than 1 per cent is excreted in the urine, indicating virtually complete biotransformation of the drug. Two metabolites have been recovered from the urine: chlorzoxazone, in which the amino group is replaced by hydroxyl; and "hydroxy-zoxazolamine," formed by the introduction of a hydroxyl group into the benzene ring. The latter compound is excreted as the glucuronide.

Zoxazolamine produced a marked uricosuric response in most gouty subjects tested. Renal clearance studies generally revealed a two and a half to three fold increase in  $C_{urate}/C_{inulin}$  twenty to forty minutes after oral administration of the

drug, and a peak four and a half to ninefold increase in  $C_{urate}/C_{inulin}$  (usually five to sixfold) in forty to sixty minutes. The uricosuric effect of a single oral dose persists for about six hours. A transitory increase in urate clearance could be elicited with very low dosage of the drug, as little as 15 mg. This is substantially less than the minimum effective uricosuric dose of any other drug tested.

The experience to date indicates a low order of toxicity of zoxazolamine in the relatively small doses required for use as a uricosuric agent. The results suggest a clinical trial of this drug in the management of gout.

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# Review

## Clinical Diagnosis of Systemic Lupus Erythematosus\*

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ALTHOUGH reports in the recent literature have given excellent descriptions of the varied clinical character of systemic lupus erythematosus [1-4], the wide experience with this disease gained during the past few years in our clinic in the diagnosis of 108 cases, and the recognition of additional diagnostic features have prompted us to report our findings.

The clinical manifestations of systemic lupus erythematosus (S.L.E.) are extremely varied, depending on the organs or tissues involved. The fact that this disorder affects almost any organ is one of its most salient characteristics. This can be better appreciated when one realizes that this disease is primarily an inflammation of the connective tissue which is so widely distributed throughout the body. Thus the protean symptomatology itself is one of the guides to diagnosis.

The main symptoms may be cutaneous, gastrointestinal, cardiovascular, renal, articular, hematological or pulmonary, among others, often in various combinations or proportions. In addition, the disease may be acute and severe with high fever, or may appear as a subacute or subdued picture. While it is hardly possible to describe all the polymorphic forms lupus may assume in any single report, we shall summarize the clinical manifestations recognized in our 108 patients.

### PRESENTING COMPLAINTS

The mode of onset varied greatly. Sometimes it was vague and insidious to such an extent that the patient found it difficult to date the onset. On other occasions, the onset was more clear-cut and was ushered in by definite joint pains, a violent erythematous rash, fever, pleuro-

pneumopathy, nephropathy or other acute manifestation.

*Symptoms of Fully Developed Disease.* This stage was characterized by one or more of the symptoms listed in Table I in the order of frequency in which they were observed.

TABLE I  
SYMPTOMS AND SIGNS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Symptoms	Cases	
	No.	Per cent
Constitutional . . . . .	108	100
Articular . . . . .	99	91.6
Cardiac . . . . .	96	88.8
Cutaneous . . . . .	88	81.4
Gastrointestinal . . . . .	67	62
Mucosal . . . . .	71	65.7
Muscular . . . . .	69	63.8
Edema . . . . .	64	59.2
Serosal involvement . . . . .	58	53.7
Lymphatic . . . . .	50	46.2
Pulmonary . . . . .	58	53.7
Mental (psychic) . . . . .	39	36.1
Neurologic . . . . .	36	33.3
Vascular . . . . .	38	33.3

The frequency of constitutional symptoms, present in 100 per cent of the patients, deserves to be stressed. The detailed enumeration of these symptoms is listed in Table II.

Fever was often high; in the acute types of the disease the temperature reached 40°C. (104°F.). It was sometimes persistent, resembling typhoid fever, more often intermittent or remittent. Occasionally, the temperature elevation was moder-

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ate, slight or even absent; the latter applied especially in chronic cases. In some instances the fever was ascribable to intercurrent infections, e.g., sinusitis, otitis, tonsillitis, cholecystitis, pyelocystitis, pneumonitis and meningitis. In general, the fever did not respond to treatment with antipyretics, sulfonamides or antibiotics.

TABLE II  
CONSTITUTIONAL SYMPTOMS OF SYSTEMIC LUPUS  
ERYTHEMATOSUS

Symptoms	Per cent Incidence
Fever.....	93
Asthenia.....	84
Loss of weight.....	74
Anorexia.....	67.5
Malaise.....	68
Headache.....	55
Insomnia.....	39.8

Onset of fever heralded reactivation or exacerbation of the disease while the patient was under treatment.

The remaining general complaints are self-evident and deserve no special comment.

*Joint Symptoms.* These were the most common local symptoms. "Rheumatism" was a frequent mode of onset, many patients being first diagnosed as having rheumatic fever or rheumatoid arthritis. This happened especially in mild and subacute cases.

Articular symptoms were present in 91 per cent of our series. These were migratory arthralgias (64 per cent), intermittent arthralgias (51 per cent), fixed joint pains (25 per cent) or permanent joint disabilities (33 per cent). Occasionally joint involvement was symmetrical, leading to confusion with rheumatoid arthritis.

All joints apparently may be involved, both small and large. In more than half the patients inflammatory signs of synovitis or arthritis were present. The disease more commonly affected the joints of the upper extremities than those of the lower limbs or other joints such as the temporomandibular or spine, etc.

In a number of patients (22 per cent) joint deformities developed. Roentgenography disclosed changes corresponding to chronic arthritis and similar in type to those of rheumatoid arthritis ("punched out" lesions, osteoporosis). The findings in synovial biopsy specimens resembled those of rheumatoid arthritis.

A noteworthy fact is that these pains were unresponsive to analgesics and current anti-rheumatic medications. On the other hand, the arthralgias generally subsided when the patient was treated with cortisone; in fact they were frequently the first symptoms to disappear. In some cases, joint pains persisted in subdued form and the patient suffered episodic exacerbations while receiving maintenance doses of cortisone.

*Cardiac Symptoms.* There were no characteristic symptoms. The most common finding was tachycardia, not necessarily proportional to the degree of fever. This was often present even in the absence of fever, or persisted after fever ceased. Occasionally tachycardia continued in spite of remission indicating, perhaps, the existence of lupus myocarditis. Loud or faint murmurs were sometimes heard over different sites of the precordium, especially in the mesocardiac area. The murmurs were generally systolic, but diastolic murmurs may be present, as in five of our patients. This finding may lead to an erroneous diagnosis of concomitant rheumatic valvulopathy or subacute bacterial endocarditis. Gallop rhythm was present in thirteen of our cases. Some patients complained of precordial pain which reflected, perhaps, the onset of pericarditis.

If all these symptoms are summed up—tachycardia, gallop rhythm, murmurs—it may be stated that 88.8 per cent of the patients in our series had some cardiac involvement. However, these symptoms consisted mostly of functional alterations which were attributable to fever, anemia or weakness of the myocardium, as could be expected from any other toxic or infectious disease.

It is well known that lupus may involve the endocardium, producing the so-called atypical verrucous endocarditis (Libman-Sacks) pathognomonic of this disease. This is characterized by soft and friable verrucae located especially along the line of implantation of valve leaflets, on both sides of the leaflet itself, and on the mural endocardium. This endocarditis does not produce clinical signs because of its location, it does not alter valve openings, and therefore usually does not of itself give rise to murmurs. It is an anatomic rather than a clinical entity [5-7]. Pericarditis is described later under "Serous Symptoms."

*Cutaneous Symptoms.* Their interest lies in the fact that they commonly constitute an important basis for the diagnosis, particularly when the skin

lesions are characteristic. Cutaneous involvement is not always present, as shown by the fact that in 18.6 per cent of the patients in our series no cutaneous symptoms developed throughout the evolution of their disease. Of those patients in whom cutaneous symptoms were recorded, some gave only a past history of skin complaints referable to S.L.E.; in others the cutaneous symptoms first became apparent during the evolution of the disease. The diagnosis was made in the absence of cutaneous symptoms in 30 per cent or more of the cases. This was especially true in some acute types of S.L.E.

The most typical cutaneous manifestation was an erythematous eruption with varying degrees of bluish discoloration, occurring particularly on exposed areas of the skin such as the face, neck, hands, fingers and, less frequently, the limbs and trunk. Skin lesions were often highly polymorphic. Isolated or confluent maculas were sometimes present. The margins were imprecise and sometimes ragged. Distant isolated lesions sometimes appeared. On close examination, dilatation and frequently plugging of follicular openings, fine superficial telangiectasias, hyperkeratosis, and small adherent or furfuraceous scales were encountered. These lesions were more characteristic of acute and subacute forms of S.L.E.

The lesions of the hand were noteworthy and deserve special mention. The palms were especially involved by erythema, sometimes mottled in appearance, of the thenar and hypothenar regions. These manifestations were nearly always symmetrical and showed a particular tendency to involve juxta-articular zones. The fingers took on a fusiform appearance due to bulging of the middle, coupled with thinning of the distal phalanx. The erythema was most intense in the nail bed where the skin appeared purplish, atrophic and frequently desquamated and ulcerated. The nails occasionally showed gnawed lateral borders and manifest thickening, the latter from the fingertips adhering firmly to the nails as a result of the intense hyperkeratosis. Some patients in our series showed pigmentation beneath the fingernails. The fingertips sometimes appeared flattened.

All these cutaneous manifestations were more or less conspicuous and of varying extent, at times limited, in other cases occupying vast areas. Thus on the face, they might involve the forehead, malar regions, eyelids, eyebrows, upper lip, ear, chin, etc., or occupy only the

bridge of the nose. The same applied to the rest of the body.

All that has been said thus far refers to the typical cutaneous lesions, the sole presence of which certifies the diagnosis of cutaneous lupus erythematosus. Apart from these, there are the atypical manifestations that have nothing characteristic about them; these include urticaria, toxic or multiform erythema, psoriasis, seborrheic dermatitis, senile keratosis, pityriasis rubra, lichen planus, scleroderma, sarcoidosis, or the Seneur-Usher syndrome. In one of our cases the dermatologist diagnosed rosacea. Occasionally purpura appeared; in combination with typical or atypical skin manifestations. Petechiae sometimes exhibited a pale center, supposedly due to capillary thrombosis. Telangiectasia and alternating pigmented and depigmented areas simulating vitiligo were occasionally present. At times the increase in pigmentation was so intense as to suggest Addison's disease at first sight. It has already been mentioned that the disease may lead to the formation of vesicles or bullae, especially on the margin of erythematous zones and particularly when there is marked edema. These blebs sometimes ruptured leaving ulcers that, on healing, produced depressed or irregular pigmented scars. All these skin lesions were characteristically painless.

The diverse cutaneous manifestations were present in our 108 patients in the following distribution: typical lupus in sixty-four patients; desquamation in thirty-nine; pigmentation in thirty-eight; hyperkeratosis in eighteen; atrophy of the skin in twenty-four; telangiectasias in ten; purpura in eleven; depigmentation in ten; vesicles in seven and crusts in five. The distribution of the lesions was as follows: diffusely over the face, fifty-eight patients; malar regions (cheeks), fifty; bridge of the nose, forty-two; ears, thirty-nine; hands, thirty-eight; lower extremities, twenty-seven; palms and fingers, twenty-four; neck, twenty-two; trunk, twenty; articular areas, fourteen; toes, five patients.

The hair changes were very interesting. Alopecia was very frequent in any of its forms, circumscribed, patchy or generalized (47 per cent). In addition, the hair was frequently coarse, dry and lusterless, resembling that of hypothyroidism. Hair growth was retarded in certain regions, especially along the anterior hair line, giving rise to short hairs which did not comb together with the rest and produced a dishevelled appearance. We believe that this

general aspect, which we designate "lupus hair," is a valuable sign in diagnosis, even on observing the patient at a distance. This manifestation was present in twenty-one of our patients.

*Diverse Gastrointestinal Symptoms.* These were frequent (62 per cent). Dyspepsia and abdominal pains were the most common. Pain occurred in various locations and was changeable, not limited to any particular region. Sometimes it was localized (twenty-three cases) and even simulated biliary colic (fourteen cases). It was located in the right inguinal region in some instances. Nausea, vomiting, tympanites and diarrhea were noted in eighteen patients. Dysphagia was observed in one case.

*Hepatomegaly* was frequent (24.4 per cent). Four of our patients had jaundice as a manifestation of the disease. One was admitted with the diagnosis of severe hepatitis, supposedly a fulminating viral hepatitis; he was treated with cortisone and recovered. Abundant Hargraves' cells were found later in the patient's blood. The evolution sometimes closely resembled that of viral hepatitis, making it difficult to decide whether jaundice had been caused by lupus or an intercurrent virus hepatitis.

*Mucosal Symptoms.* The mucosae became involved especially in the acute and subacute types. The site of predilection was the mouth. Eruptions, hemorrhages, small erosions or ulcers (sometimes of a herpetic type) were situated predominantly on the gums, lips and soft palate where often groups of small petechiae also were seen. Secondary infection sometimes supervened, giving rise to stomatitis, gingivitis and cheilitis. These lesions were occasionally covered by diphtheroid exudate and, on healing, left whitish patches that resembled leukoplakia.

*Changes of the conjunctivas* were particularly important. Hyperemia and anterior polaritis were sometimes present. On other occasions, hemorrhages were noted, particularly in the scleral conjunctivas. The most peculiar finding was edema of the bulbar conjunctivas which, if intense, produced prominent folds of the conjunctivas (chemosis) which give the eye a peculiar appearance. The incidence of this sign was low (20 per cent) but we consider it of great value in diagnosis. Its presence, particularly if accompanied by other suspicious findings (arthralgias, constitutional symptoms or signs of visceral involvement), is highly suggestive of lupus. Edema of the eyelids will be discussed later.

*Muscular Symptoms.* Muscular pains, generalized or localized, spontaneous or after exertion, were very common. Hypotonia and atrophy also were found. Muscular complaints, in general, were noted in 63.8 per cent of our cases. Muscular atrophy was either widespread, confined to a particular muscle group, or affected diverse muscle groups with varying intensity. These symptoms often made the differentiation between lupus and dermatomyositis difficult.

*Edema.* This was frequent. It was found predominantly about the ankles, but also involved the eyelids, the lumbar region, the face or became generalized. It was frequently associated with erythema, telangiectasia or other cutaneous lesions. This happened especially in palpebral edema. It affected both upper and lower eyelids and occasionally spread to the rest of the face. Edema was present in sixty-four of our 108 patients but in nine of these there were concomitant signs of phlebitis so it may have been produced by this latter condition.

Six edematous patients presented a nephrotic syndrome with proteinurias in excess of 5 gm. per day and marked hypoproteinemia. Strangely enough, in two of these patients necropsy revealed no alterations of the kidney worthy of note.

*Serous Symptoms.* Serosal involvement occurred in 53.7 per cent of our cases at some time during the course. Frequently several serous membranes were simultaneously affected, constituting a polyserositis. There were pleural and/or pericardial effusions, and ascites. In some instances the serosal lesions, apparent only at postmortem examination, consisted of fibrous plaques, exudates or adhesions which had produced no clinical manifestations.

The pleural membrane was the most commonly involved serosa, as forty-nine of our patients presented symptoms of pleural involvement and in seven other patients necropsy revealed lesions. Thus, the pleurae were affected in 56.6 per cent of our series. Undoubtedly pleural involvement must be even more frequent. Our data are limited by the fact that autopsy has been performed so far in only twenty-five of the 108 cases. Diagnostic thoracentesis revealed purulent fluid in two of the ten cases in which it was carried out, and a serofibrinous or serosanguinous effusion in the rest. The lymphocyte content of the cells found in the fluid varied from 40 to 90 per cent. L.E. cells were not observed in this exudate.

It is worthy of note that pleural involvement was bilateral in approximately half the cases in which it was present. This characteristic is, in our opinion, of great diagnostic importance [8].

Pericarditis was diagnosed clinically in thirteen cases. Seven more cases were discovered at autopsy. It was a dry or fibrinous inflammation without specific characteristics. In order to diagnose lupus pericarditis one must be alert for such symptoms as precordial pain increased by breathing, dyspnea, and even dysphagia; and findings such as a pericardial friction rub or enlargement of the heart, when effusion is present. Such signs were noted in four of our cases. Aspirated fluid was serofibrinous in two cases, and purulent but aseptic in one.

Peritoneal serositis was less frequent. It may conceivably be the real cause of many of the abdominal complaints (discomfort, tympanites, diffuse or localized pain). Ascites was present in sixteen of our cases. Usually it was scanty and could easily have been overlooked. Dry or fibrinous peritonitis, in the form of perisplenitis, perihepatitis or fibrous adhesions, was more common. Clinical diagnosis of these peritoneal irritations was impossible, but such lesions constituted a common autopsy finding [9].

*Involvement of the Lymphatic System.* This was manifested fundamentally by lymphadenopathy and splenomegaly. Less than half the patients showed lymph node enlargement (46.3 per cent). The glands involved in order of frequency were: cervical, submaxillary, axillary, supraclavicular. Inguinal adenopathy was less common. Nodes were small, painless, hard, and devoid of inflammatory characteristics, non-adherent to superficial or deep planes except in one of our cases. At times they became more enlarged and led to confusion with Hodgkin's disease. The lymph nodes were never very large. Neither did they tend to form fistulas or become softened.

Splenomegaly was noted in 19.4 per cent of our cases. It was always moderate in degree, sometimes scarcely detectable by palpation or percussion. Occasionally it was only an autopsy finding. In connection with splenomegaly, one must bear in mind that thrombocytopenia is frequent in lupus, and purpura simulating Werlhof's disease may occur [1,2]. Two of our patients underwent splenectomy because of this diagnosis. One of these patients showed improvement which lasted for two years, followed by the appearance of the full symptom complex of systemic lupus erythematosus. He was

treated with cortisone and his manifestations remitted; he is still in fairly good condition. The other patient died one year after the apparent cure that ensued upon splenectomy. Necropsy confirmed the diagnosis of lupus. In the light of our experience, the presence of a markedly enlarged spleen militates against the diagnosis of lupus.

*Pulmonary Symptoms.* In fifty-eight cases (53.7 per cent) we found unilateral or bilateral pulmonary lesions associated with dyspnea and cough either of the non-productive type or accompanied by sputum of diverse characteristics. Hemoptysis was rare. Areas of congestion occasionally simulated pneumonia. Radiologic study confirmed the existence of foci of condensation and sometimes revealed densities that were larger in size than would be expected from physical findings. At times, roentgenologic findings were less marked than those of physical examination, probably because the pathological process was interstitial. All these pulmonary lesions followed a protracted course which might last months, and upon which antibiotic therapy generally exerted no influence.

Dyspnea may occur in lupus in the absence of clinically or radiologically demonstrable alterations in the lungs, what has been designated as "dyspnea sine materia" [10]. The association of dyspnea with arthritis, skin lesions or other suspicious manifestations may play an important part in helping to establish the diagnosis.

*Neurologic Symptoms.* There were a great variety: convulsions, hemiplegia, polyneuritis, paralyzes, disturbances of the motility of the bladder, and other neurologic manifestations. These symptoms have been attributed to vascular alterations of the brain, spinal cord or peripheral nerves. Since involvement of the circulatory system in this disease is so variable, it is not surprising that neurological manifestations may be so protean. We have not found neurological symptoms as frequent as has been claimed by other authors. Undoubtedly this must be because we did not search for them with enough diligence in the beginning, and we did not perform routine lumbar puncture and electroencephalograms. In spite of this, we have found symptoms in thirty-six patients (33.3 per cent) consisting of: paresthesias in thirteen, neuritis in eight, cranial nerve palsies in six (paralysis of the palate, abducens, levator palpebrae, and the like), epileptiform or Jacksonian seizures in nine, and dysarthria in two. One patient who had been

receiving cortisone therapy for one year presented a myelitis with flaccid paraplegia, associated with sphincter incontinence. He has improved to a certain extent from both disturbances but is still confined to his bed because of weakness of his lower limbs. Sphincter incontinence was commonly observed in the final stages of the disease in other patients.

*Psychic Symptoms.* Thirty-nine patients presented psychic manifestations consisting of excitement, uneasiness, anxiety and, occasionally, delirium. Symptoms of depression were less frequent (dullness of the sensorium, indifference, disorientation, and the like).

*Vascular Symptoms.* The blood pressure was normal in most of the patients. Two patients with acute disease had blood pressure readings of 190/140 mm. Hg. Four patients with subacute and two with chronic disease presented hypertension of moderate degree.

In both acute cases with hypertension there was marked renal involvement, with proteinuria of more than 1 gm./L. The same coexistence of high blood pressure and urinary abnormality was observed in the subacute cases. Thus, in all cases with hypertension there was renal involvement, but the opposite correlation did not hold true, since in many of our cases with renal involvement, even of marked degree, hypertension was absent [11,12].

Thirteen patients presented manifestations of thrombophlebitis or phlebothrombosis. We did not look for them systematically at first so we may have missed some instances. It is well known that a careful search must be made for phlebothrombosis in order to diagnose it. On the other hand, autopsy data are not reliable because the veins usually are not thoroughly examined.

*Raynaud's phenomenon:* It is interesting to point out that this syndrome sometimes precedes the onset of the visceral symptoms of the disease. This happened in seventeen of our cases (15.7 per cent). Raynaud's phenomenon was more common in chronic cases, in which it often was associated with articular symptoms. In four of our patients these vasomotor phenomena of the hands began several years before any other symptoms, and continued throughout the entire course of the disease. Raynaud's syndrome beginning in summer with concomitant visceral symptoms is of special significance in diagnosis [13].

*Eyeground changes:* These were described long ago by Maumenee [14] who established several

distinct types. Eyeground changes have been frequent in our series, occurring in twenty of sixty-six patients in whom funduscopy was performed. The most common finding was the nodular cotton-wool exudate (16.6 per cent). Hyperemia of the disc coupled with dilated and dark veins was noted in 9 per cent [15]. There was retinal edema in eight cases and papilledema was present in two. Three patients showed small hemorrhages about the optic disc.

*Laboratory Findings.* Routine performance of certain laboratory studies, especially hematologic study and urinalysis, reveals abnormalities which are important in establishing the diagnosis.

*Hematologic phenomena of systemic lupus erythematosus: The L.E. phenomenon.* The discovery of "L.E." or Hargraves' [16] cells represents the most important contribution that the laboratory has made in the diagnosis of S.L.E. Although still a subject of some minor differences of opinion, typical L.E. cells are considered by most authors to be specific for this disease [17].

This test was available to us in our last ninety-two cases of lupus, and a positive L.E. phenomenon was found in eighty-three (90.4 per cent). Since the test is so valuable in confirming the diagnosis of S.L.E., and particularly since the care taken in examining the slides and the method used by various authors has differed, it seems important to describe our technics. Doctors Ducach and Granic have reported these in detail elsewhere [18], but a brief reiteration follows.

L.E. cells were originally described in heparinized bone marrow obtained by sternal puncture [16], later in peripheral blood [17]. We have found these cells most conveniently in the centrifuged clot of peripheral blood [18]. The preparations are made by several methods: that of Zimmer and Hargraves [17], Snapper [19] and Sockley [20]. The number of positive tests obtained by these methods is sufficiently high to make marrow aspiration unnecessary.

A positive L.E. phenomenon may be manifest in at least one of several ways. The finding of multiple typical L.E. cells: mature neutrophile leukocytes containing a large amorphous mass, round or oval in shape, of a diameter between one-third that of an erythrocyte and four times the size of an erythrocyte, which stain purple or reddish brown, and contain no chromatin structure. This mass displaces the nucleus of the granulocyte to the periphery, giving a ring-like appearance to each cell. If the amorphous

mass is surrounded and partly engulfed by two or more granulocytes the so-called "rosette" phenomenon is seen. In addition, at times there are non-phagocytosed amorphous masses—so-called "free amorphous masses" or "globes"—which in our opinion as well as that of most authors have the same diagnostic value as the first two manifestations. So-called "tart cells" are not considered diagnostic for S.L.E., as we have found them in many other diseases; so these are regarded as "atypical" but they are of some interest since they may be the sole remaining element found in the blood after typical L.E. cells have disappeared during remission.

In our experience there has been no correlation between the presence of L.E. cells and the prognosis, since they have been seen in some of our asymptomatic cases, yet were absent in some of our severe and fatal cases. A positive L.E. phenomenon may persist during treatment or in remission longer than any other laboratory test [21] and may therefore be considered a faithful index of the disease.

*Hematologic findings:* Examination of the blood frequently reveals alterations which, although not specific, may aid in the diagnosis. The following findings are common; secondary anemia, absolute and relative leukopenia, and thrombocytopenia.

*Anemia* was present in 60 per cent of our patients. It was usually of the secondary type, normocytic and normochromic. Hypochromic anemia was rare. The anemia was of varying severity. S.L.E. may produce hemolytic anemias of the acquired type [22,23]. We recently had an interesting case of acute hemolytic anemia in which the Coombs' test (direct and indirect) was positive, and an "incomplete" agglutinin subject to activation by trypsin was demonstrated. Two other patients without hemolytic anemia had a positive Coombs' test. These two patients had circulating cryoglobulin as well. These findings may help to explain the violent post-transfusional reactions that sometimes occur in these patients, as due, conceivably, to activation of circulating antibodies of the host by the fresh complement supplied by the transfused blood.

*Leukopenia* is common (43.5 per cent). The leukocyte count generally lies between 2,000 and 5,000 cells per cu. mm., fluctuating greatly during the course of the disease. The white blood cell count varies, especially when complications occur. Thus it is not rare to see the count reach 10,000 or 12,000 per cu. mm. with intercurrent

infections or respiratory pathology. At times a high leukocyte count was found with no apparent reason, except possibly due to the disease itself. Leukopenia was especially valuable as a diagnostic aid when present in febrile patients who commonly show an elevated white count. A shift to the left in the differential count was almost always found.

*Thrombocytopenia* was less frequent. At times it took on the clinical disguise of Werlhof's disease. Two of our patients in whom the disease began in this way underwent splenectomy which produced transient improvement, but later a full-blown S.L.E. developed. This may possibly be related to immune phenomena, similar to those described in the hemolytic anemias. Not all hemorrhages in lupus were attributable to a low platelet count. Some appeared to be caused by vascular factors. It is also possible that some might have been due to circulating anticoagulants, as occurred in one of our cases [24].

*The erythrocyte sedimentation rate* was elevated in 94.4 per cent of our cases (considering the total course). It usually decreased during spontaneous or therapeutic remissions [25]. Values were often very high; in eleven cases it surpassed 100 and in three it rose above 140 mm. in the first hour.

We have found *altered flocculation tests* (cephalin flocculation, thymol, colloidal red, Poirier blue, China ink). Positive tests were found in 79 per cent of the patients. Beyond doubt, this was due to the very frequent changes in the serum proteins. Fatty infiltration of the liver—often accompanied by foci of centrilobular necrosis—may perhaps have played a role as well.

*The serum proteins* were commonly altered. The usual finding was a normal or slightly diminished total protein, coupled with an increased globulin and decreased albumin content. Hyperglobulinemia was the most characteristic change. Gamma globulin was most increased; but the alpha 1 and 2 fractions showed an increase as well, while the beta fraction decreased or remained at levels near normal. These findings have been confirmed in our cases by electrophoretic studies [26].

*False positive serologic tests* may be present in lupus, attributable to the same protein changes. The proportion of false positive tests for syphilis recorded by different authors varies from 9 to 87 per cent. It occurred in only 9 per cent of our series.

*Blood cultures* were negative, as were agglutination reactions.

The renal involvement was of utmost importance. The changes found on urinalysis coincided, in general, with those found in the nephritides: proteinuria, hematuria, cylindruria. Two characteristics of the urinary syndrome were noteworthy: its persistence, and the little tendency to produce marked renal insufficiency. We found urinary changes in 76.8 per cent of our cases. Proteinuria was the most common finding. We have only considered frank proteinurias (0.50 gm./L. or more). The values fluctuated from marked traces of protein to proteinurias of 12 gm./L. Proteinurias above 2 gm./L. were frequent. In eighteen cases the figures exceeded 5 gm./L. in one or more urinalyses. Proteinuria was sometimes intermittent but it was more commonly permanent. Hematuria was also frequent, fluctuating between 1 to 4 plus. Cylindruria was found in approximately half the cases. In our series 13.8 per cent of the patients presented definite renal insufficiency with a blood urea nitrogen of more than 100 mg. per cent. In three patients the values were over 400 mg. per cent in the premortem stage and in two others 280 and 250 mg. per cent, respectively. Both of these last patients died in uremia. In thirty-five of the patients in whom the blood urea nitrogen was determined, this surpassed 50 mg./100 ml. There were definite renal symptoms in thirty-three of these patients. Renal involvement was more manifest in acute and subacute cases but rarely (six of our cases) simulated a nephrotic syndrome.

The urinary output of 17 ketosteroids was low. In 82 per cent of the twenty-eight cases in which they were studied, the values obtained were below 4 mg./twenty-four hours.

#### DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

The diagnosis is often difficult because this disease is protean and changeable. The disease has no pathognomonic symptoms and its various symptom complexes may make their appearance at different times during the course, often leading to the confusion of clinicians.

We have thought it helpful to establish certain symptom associations that highly suggest lupus, as an aid to the diagnosis of a disease of so varied and widespread a symptomatology. In our experience, they have proved very useful. Thus we believe the diagnosis of S.L.E. should be proposed in the following conditions:

1. *Arthropathies* that follow a strange course, i.e., in all cases of "rheumatism" with unusual

findings such as disproportionate fever, marked constitutional symptoms, signs of nephritis, serosal involvement, associated pneumopathies, alopecia, Raynaud's syndrome, lymphadenopathies, etc.

2. *Atypical nephropathies*, particularly if they are febrile. An even more suggestive combination is that of nephritis with arthritis, which rarely occurs in the classic nephritis, or with pleural symptoms.

3. *Polyserositis or pleurisy*, especially if it is bilateral, accompanied by other unusual manifestations such as nephritis, arthritis or any of the other symptoms already mentioned.

4. *Prolonged fever of undetermined etiology*, especially if it coincides with any of the other syndromes that have been mentioned.

5. *Raynaud's syndrome*, especially if it begins in summer and is accompanied by fever, nephritis, arthropathy, serosal involvement or pneumonitis. Admittedly, Raynaud's syndrome in scleroderma may be associated with arthritis but there are other characteristic skin manifestations.

6. *Chemosi*, unexplained by local or general causes. Edema of the conjunctivas may be produced by ocular diseases, generalized edema of significant degree, allergic or drug reactions, or severe anemia. But in general this sign, in the absence of an obvious cause, has been of great help in leading to the diagnosis of lupus. In fact, in several of our patients the first manifestation that pointed to the diagnosis was chemosis [11].

7. *Any alopecia* associated with hair changes compatible with those described under what we have designated "lupus hair."

8. *Dyspnea "sine materia."*

9. *Changes in the eyegrounds* not explained by hypertension, diabetes or nephropathy.

If the diagnosis is suspected in the presence of any of these symptom-complexes a very painstaking examination of the skin should be made. This will often reveal slight changes that might otherwise go unrecognized. It must be borne in mind that the cutaneous lesions are not always typical, and also that those signs present at the moment may be nothing but residual changes, such as dyskeratosis, follicular plugging, pigmentation, desquamation, etc. In some cases atrophic, thin and brilliant skin, similar to silk paper, may be seen as a result of the cicatricial process. Even the most experienced dermatologists may miss the diagnosis of the cutaneous manifestations at times. Some of our cases were

diagnosed as psoriasis by very qualified specialists. Many cases that we initially classified as lupus "sine lupus," on being re-examined with the diagnosis in mind, had to be reclassified as cases with cutaneous symptoms.

The laboratory findings that have provided assistance in diagnosis include: (1) Erythrocyte sedimentation rate, which becomes altered in 94.4 per cent of the cases. (2) Flocculation tests, positive in 79.7 per cent. (3) Changes in the serum proteins. (4) Anemia (60 per cent). (5) Leukopenia, present in 43.5 per cent of the cases. (6) Thrombocytopenia. (7) Hemolytic anemia.

Beyond doubt, the most important laboratory finding is that of Hargraves' cells and the hematologic phenomena of S.L.E. Some authors estimate that the test is positive in 100 per cent of the cases, others in 60 to 80 per cent [2,30]. We have found the typical L.E. phenomenon in eighty-three of our last ninety-two cases, or 90.4 per cent. It is difficult to calculate with what frequency the test is positive in lupus because there is no clinical method for certifying the diagnosis when the Hargraves' test is negative. Undoubtedly there must be cases in which the diagnosis is not made because the test is negative. For this reason we can speak only of "apparent" frequency and not of "real" frequency. There are cases which clinically and accordingly to the laboratory data correspond to lupus, in which the L.E. test is negative. This occurred in three of our cases, in which autopsy confirmed the diagnosis of lupus beyond doubt. Therefore, we are now certain that there are cases of lupus in which the L.E. phenomenon is always negative, for which reason we consider that this phenomenon, although very frequent, is not a *sine qua non* for the diagnosis. We also wish to point out that the phenomenon, having been negative in the beginning, became positive late in the course of the disease, even during cortisone treatment, in three cases. If these patients had not been carefully followed-up they would have increased the number of "proved cases with negative L.E. phenomenon." On the other hand, one of our cases, which clinically appeared to be typical of S.L.E. but with persistently negative L.E. cell examinations, on necropsy was shown to have polyarteritis nodosa.

We believe that there is no correlation between the number or aspect of the L.E. cells and the type of course or the prognosis of the

disease. Thus, even though L.E. cells are definitely more numerous in acute than in chronic forms of the disease, this is not constant and we have seen chronic cases with 35 or more per cent of L.E. cells. Besides, the number of L.E. cells may increase considerably in chronic cases when there are exacerbations or intercurrent febrile diseases.

Most authors have concluded, after studying the L.E. phenomenon in "collagen" as well as in other diseases, that it is positive only in lupus [2,30-33]. Nevertheless, there is no general agreement and some authors claim that they have found positive L.E. tests in herpetiform dermatitis, miliary tuberculosis, amyloidosis, generalized moniliasis, rheumatoid arthritis, chronic nephritis, hepatic cirrhosis, leukemia, pernicious anemia, epilepsy and multiple myeloma. Even in these cases, when the blood smears have been reviewed by very qualified investigators, the cells in most instances have been shown to be atypical, a fact which demonstrates once more that the experience of the hematologist is fundamental in the evaluation of the phenomenon.

The specificity of the test has been questioned because cells have occasionally been discovered in cases of hypersensitivity to penicillin [34]. This is debatable since these may have been cases of lupus in which cells could have been present before penicillin administration. It is known that penicillin and the sulfonamides produce exacerbation of subclinical cases of chronic lupus. It is possible that the phenomenon may appear in hypersensitivity reactions which, in our opinion, are difficult to separate from authentic cases of lupus. That is to say, these hypersensitivities to penicillin could simply be considered "lupic reactions" or, as Hargraves has designated them, "lupic diatheses" [35].

The same phenomenon has been observed in patients treated with hydralazine [36], and after treatment with estrogens or on withdrawal of steroid therapy [37] in cases of rheumatoid arthritis. This we have also observed.

In an effort to elucidate this problem we have performed 675 L.E. cell investigations during the last year (mostly by the clot technic) in 400 patients suffering from various diseases: S.L.E., rheumatoid arthritis, rheumatic fever, nephritis, hematologic disorders, especially hemolytic anemias and thrombocytopenic purpuras, and "collagen disease" other than lupus. The test was positive in thirty of the thirty-one cases of

S.L.E. One or more examinations were performed in ninety-one cases of rheumatoid arthritis. In sixteen cases (17 per cent) phagocytosis of nuclei was present and in five (5.5 per cent) typical L.E. cells were found in small numbers. There is still some doubt as to whether these are authentic cases of rheumatoid arthritis or are cases of S.L.E. of the "rheumatic type." The L.E. cell test was negative in three cases of scleroderma, two of multiple myeloma and one of sarcoidosis. In two cases of polyarteritis nodosa, one was found to be negative and the other dubiously positive in four examinations.

Our impression is that the finding of an important number of typical L.E. cells or of "globs" in a patient not receiving hormone therapy and with clinical evidence that points to the diagnosis of S.L.E., certifies the diagnosis. In this situation L.E. cells are specific. On the other hand, the presence of sparse typical or atypical cells does not confirm the diagnosis of S.L.E.

The differential diagnosis must be made especially with respect to the following diseases: (1) rheumatoid arthritis, (2) rheumatic fever, (3) Hodgkin's disease, (4) subacute bacterial endocarditis, (5) extrapulmonary tuberculosis, (6) Raynaud's disease, (7) other "collagen diseases" such as scleroderma, dermatomyositis and polyarteritis nodosa. The greatest difficulty lies in the differentiation from rheumatoid arthritis since there is a great deal of overlapping between them. Hodgkin's disease may create serious difficulties in differentiation. The differential diagnosis from other "collagen diseases" presents many problems. The clinical picture of many of these "diffuse collagen diseases" is also varied many times with symptoms overlapping those described for lupus. Differentiation in many such cases is only made by waiting for the full-blown typical clinical pattern to develop, or by the finding of repeatedly negative "L.E." preparations.

#### SUMMARY

The clinical features noted in 108 cases of systemic lupus erythematosus diagnosed in our clinic are described in detail. As a result of this experience, emphasis is placed on the extremely varied nature of the clinical picture. We deem several features important in clinical diagnosis that have received relatively little notice in other reports. Among these are certain skin lesions, "lupus hair," chemosis, bilateral pleurisy and

dyspnea "sine materia," which were fairly common and helpful in suggesting the diagnosis in our patients.

The diagnosis of lupus cannot be made with certainty from the clinical picture alone, but symptom complexes such as prolonged fever of undetermined origin; polyserositis or bilateral pleurisy; "summer Raynaud's phenomenon" associated with arthritis and marked constitutional symptoms; chemosis without obvious local cause; unexplained dyspnea; or anemia with normal or decreased white count without apparent cause, together with proteinuria, create a strong suspicion of systemic lupus. The most dependable diagnostic test is the demonstration of the "L.E." phenomenon in the peripheral blood clot.

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# Seminar on the Brain

## Biochemical Aspects of Cerebral Dysfunction\*

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STUDIES of the biochemical aspects of the conditions in the body that lead to cerebral dysfunction are important for our understanding of the functional behaviour of the central nervous system and its relationship to mental processes. Recent events in the neuropsychiatric domain have led many who were formerly indifferent or even antagonistic to the concept that chemical, or physicochemical, mechanisms may underlie abnormal mental behaviour to the realization that changes of metabolic processes in nerve cells may result in symptoms characteristic of a number of mental disorders. Various hypotheses, which form the bases of new experimental work, and which attempt to correlate the metabolic effects of neurotropic drugs with the clinical findings in the psychoses, have been suggested [1].

A recent survey [2] has shown that neurological disturbances may be brought about by: (1) substances that affect the energetics of the nerve cell by interference with oxidative phosphorylations or by effects on stimulated neuronal respiratory processes (such compounds include a wide variety of narcotics, tranquilisers, alcohols, aldehydes and steroids); (2) substances that interfere with the transport of metabolites, e.g., amino acids, into the brain cells; (3) substances that interfere in a specific manner with brain enzyme systems, e.g., amine oxidase, DPN-ase.

The disorders that give rise to mental aberrations of an unquestioned organic origin are the degenerative diseases (including aging phenomena such as senile dementia, and the demyelination diseases); diseases of infectious origin (general paresis, encephalitis); cerebral neoplasms or traumas; epileptic disorders; endocrine and nutritional disorders (e.g., pellagra); the "toxic" disorders due to alcohols, bromide,

carbon disulphide, organic-metallo compounds, and a large variety of neurotropic drugs. To these must be added the diseases affecting the nervous system that are genetically controlled, e.g., phenylketonuria, and those cerebral disorders consequent upon the malfunctioning of various organs of the body (e.g., hepatic coma, bilirubin encephalopathy). Apart from these are the great group of psychoneuroses and psychoses, in which a metabolic etiology may ultimately be found.

It is proposed to discuss some of the salient features of the biochemical abnormalities that lead to or are associated with cerebral dysfunction. No attempt will be made, within the compass of this article, to deal even briefly with all conditions that lead to cerebral dysfunction.

*Neurolipoidosis* [3]. Sphingolipids probably play a significant role in the metabolism of the developing brain. They are almost exclusively constituents of the nerve sheaths and appear with myelination. They accumulate in the white matter of brain and spinal cord where they ultimately constitute almost half the total amount of lipids. The following diseases are considered to be lipoidoses of the developing brain: the acute infantile form of Gaucher's disease, Niemann-Pick disease, amaurotic family idiocy of the Tay-Sachs type, Pfaundler-Hurler's disease.

Gaucher's disease is regarded as being due to a disturbance of metabolism of the reticular tissue, the nervous tissue being involved, usually, only in the acute infantile form. There is extensive degeneration of the nerve cells. Most studies have been confined to the spleen, liver and lungs of patients with Gaucher's disease, where the typical lipid-containing Gaucher cells are found in large numbers. The lipid stored in the typical

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Gaucher cell is thought to be a galactocerebroside. Thannhauser et al. [4] found both galacto- and glucocerebrosides in the spleen of an infant with Gaucher's disease. Klenk et al. [3,5] found mainly glucocerebrosides in a number of patients, but in an infant with typical pathologic changes of the brain Klenk [5] obtained only galactocerebrosides. Little is known of the biochemistry of the disorder.

In Niemann-Pick disease the nervous tissue exhibits characteristic changes, the lipid stored being sphingomyelin. This holds not only for the nerve cells but for the Pick cells in liver and spleen. There are, however, certain chemical differences between the fatty acid components of the sphingomyelin of the different tissues. In the sphingomyelin of spleen and liver, lignoceric acid, behenic acid and nervonic acid are the main components of the fats whereas in the brain sphingomyelin stearic acid predominates. Niemann-Pick disease occurs most frequently in infancy, the children dying within the first two years of life. There are, however, juvenile and adult forms of the disease.

In infantile amaurotic idiocy blindness, due to optic nerve atrophy, develops and idiocy, coupled with complete paralysis, takes place in about two years with a fatal result. The condition was first described by Tay [6] and Sachs [7], and Slome [8] showed that the disease is controlled by a single recessive gene. It differs from the infantile form of Gaucher's and Niemann-Pick disease in that only the brain and nervous tissue are involved. Klenk et al. [3,5] found in cases of infantile amaurotic idiocy about ten to twenty times the normal content of gangliosides, which are closely related to the sphingomyelins and cerebrosides. The carbohydrate group of the gangliosides contains galactosamine, glucose, chondrosamine and neuraminic acid. Stearic acid is the main constituent of the fatty acids present.

Pfaundler-Hurler's disease (gargoylism) is often regarded as a special form of amaurotic familial idiocy, the disturbance in the development of the brain being accompanied by a disturbance in skeletal development. There seems to occur an increased production of gangliosides in the nerve cells and Brante [9] has observed that in tissues other than nervous tissue there seems to be an accumulation of a mucopolysaccharide related in structure to the carbohydrate group of the gangliosides. Klenk [3] considers that since mucopolysaccharides

play an important role in skeletal composition there would seem to be a connection between the main symptoms of the disorder, namely disturbances in the development of nervous tissue and of the skeleton.

The disorders that have been mentioned are inherited. They are metabolic aberrations controlled by genes. Little is known about the underlying causes of the metabolic disturbances. Possibly there is absence of a specific enzyme normally present in cerebral metabolism [3]. Sobotka [10] considers that the essential feature of the lipidoses is the absence of specific esterases that normally convert one lipid into another, whilst Thannhauser [11] suggests that coenzymes involved in the normal transformations may be missing. It is evident that the diseases most frequently involve disturbances in the metabolism of the sphingolipids. It is presumably in this biochemical field that future advances in our knowledge of these interesting and important cerebral diseases will be made.

**Demyelination.** The development of the myelin sheath (myelination) and its breakdown in pathological conditions (demyelination) are not yet well understood. Demyelination [12] has been studied in a variety of ways. Investigations have often been made of the substances, or tissue emulsions, that can produce demyelination in experimental animals, or of the abnormal dietary conditions under which demyelination can occur. Studies have also been made of demyelination *in vitro* by the application of enzymes, and of the chemical changes found in experimentally induced demyelination (notably Wallerian degeneration). On administration to animals, respiratory poisons such as cyanide, sodium azide and carbon monoxide give rise to demyelination. The administration of other metabolic inhibitors such as fluoracetate, hydroxylamine and narcotics produce pathological changes in the nervous system. These lesions, however, are not confined to white matter and are not primarily demyelinating [12,13]. Tetanus toxin [14] and Clostridium toxin [15] also induce demyelination. Anoxia produces pathological changes the relation of which to human demyelinating disease has been frequently discussed [16]. Triorthocresyl phosphate will produce demyelination, particularly in chickens [17], and the possibility [18] has been considered that the pseudocholinesterase of nerve (which is inhibited by this phosphate ester) is involved in the maintenance of the

myelin sheaths of nerve fibres. Paralytic effects due to certain organophosphorus compounds, used as insecticides, may be partly due to pseudocholinesterase inhibition and possible accompanying demyelination.

The importance of nutritional factors in the process of demyelination has been emphasized by Rossiter [12]. The well known demyelinating condition of newborn lambs termed *swayback*, or *enzootic ataxia*, is associated with low concentrations of copper in the pasture and in the blood and liver of the parent ewe and of the affected lamb [19]. Feeding small amounts of copper prevents development of the condition. The inference is that copper plays a significant role in the process of myelination and that demyelination may be caused by interference with specific enzymatic processes. Phospholipid synthesis in liver is known to be much affected by the changes induced in the cells by copper deficiency [20]. Moreover, the liver mitochondria of animals kept on a copper-deficient diet show far less respiratory activity than those prepared from a normal animal [27]. There is no evidence that copper deficiency plays any role in multiple sclerosis; nevertheless copper ions are likely to be involved in the metabolic events that lead to myelination and demyelination.

The chemistry of myelin breakdown that accompanies Wallerian degeneration has been intensively studied. Johnson et al. [23] have pointed out that Wallerian degeneration is characterized, at first, by physical disintegration of the myelin sheath with but little breakdown of the myelin lipids. There are marked changes in metabolism (e.g., failure of the nerve to synthesize acetylcholine, and nucleic acid changes) and loss of ability of the nerve to conduct an impulse. There then takes place a rapid disappearance of myelin lipids with concomitant enzymatic changes and altered ratios of nucleic acid components, and finally the myelin sheath almost entirely disappears, the Schwann cells occupying the spaces left by the degenerated sheath and axon. It is possible, according to Rossiter [12], that the destruction of myelin that takes place in the degenerating nerve is due to an enzyme system derived from a type of cell which is present in large numbers during the degenerating process. Two types of cell are suggested as responsible: one is the macrophage, the other the proliferating Schwann cell.

*Effects of Venoms.* It is useful, whilst discus-

sing the importance of lipids of the nerve cell for the organization and functional activity of the nervous system, to refer to the neurotoxic effects of certain snake venoms. The colubrid class of venoms (of which the Indian cobra is an example) have pronounced effects on the nervous system. Victims of these snakes die usually through paralysis of the respiratory muscles. Many venoms have effects on muscle similar to that of curare. They are, however, direct effects of venoms on the central nervous system. The possible role of lecithinase and lysolecithin in the neurological symptoms of venom poisoning was first suggested by Houssay et al. [24], and various findings [25] have indicated the probable identity of lecithinase with the neurotoxic factor of *Crotallus* and of cobra venom. Morrison and Zamecnik [26] have pointed out that exposure of spinal cord or brain to cobra venom, or to the alpha toxin of *Clostridium welchii*, gives rise to demyelination, the suggestion being that the lecithin of the myelin sheath is broken down to lysolecithin. Phosphosphingoside, which is present in the myelin sheath, is also hydrolyzed by the alpha toxin of *Cl. welchii*. It is reported [27] that demyelination can be brought about by substances with a detergent-like action on the myelin (e.g., by saponin or sodium taurocholate) and it is conceivable that lysolecithin may have a similar effect.

Venoms that have been heated to destroy all enzymes but the lecithinase A present retain about half their original toxicity and produce marked lesions in the nervous system [28]. Exposure of brain cortex slices to venom lecithinase A in the presence of glucose results in changes of respiratory rates very similar to those obtained when brain mitochondria [29] or brain homogenates [30] are exposed to the enzyme. Changes in respiratory rates and marked falls in oxidative phosphorylation rates take place. The conclusion is that brain cell membranes as well as those of the mitochondria contain phospholipid groups that may be attacked by venom lecithinase and that metabolic activities associated with or controlled by the membranes are thereby affected.

The enzymes that operate in phospholipid synthesis and breakdown are now becoming recognized [22]. The manner in which these are concerned with myelination and demyelination phenomena have still to be elucidated. The relationships between cerebral dysfunction and the demyelination phenomena brought about

by neurotoxic substances (or conditions) are clearly subjects for further studies.

*Inherited Cerebral Disorders.* The disturbances in cerebral function due to the lipoidoses, already referred to, are hereditary. Another inherited biochemical abnormality associated with mental defect is phenylketonuria, in which phenylpyruvic acid is excreted in the urine [33]. Still another is Wilson's disease, hepatolenticular degeneration, which is also a cause of mental defect, which is characterized by a disturbance in copper metabolism [34]. In phenylketonuria absence of phenylalanine from the diet improves the mental state of patients [35]. No definite relationship has been found, however, between the severity of the mental affliction and the phenylalanine and tyrosine plasma levels or the urinary phenylalanine and phenylpyruvic acid excretion. The reason for the association of mental deficiency with the condition of phenylketonuria, in which the metabolic defect is a decreased ability of the liver to oxidize phenylalanine to tyrosine, is at present quite obscure. It is possible, however, that new light will be thrown on this phenomenon by the finding [36] that both L-phenylalanine and phenylpyruvic acid inhibit tyrosine metabolism and may, therefore, interfere with hormone production from this amino acid.

In galactosemia, in which mental defect occurs, restriction of galactose from the diet leads to improvement in their symptoms and relief from mental deficiency. Even in patients aged one year some (although less) mental improvement may be achieved. The impaired ability to metabolize galactose has been shown to be due to the lack of a galactouridyl transferase [37]. A defect in the synthesis of this enzyme in galactosemia has been postulated.

Idiopathic hypercalcemia of infancy with mental defect has been described and held to be due to a disturbance of cholesterol metabolism with the production of derivatives with a hypercalcemic action [38].

Some forms of creatinism have been traced to specific defects in iodine metabolism, e.g., absence of an oxidase converting iodide to iodine [39], and failure to conjugate iodo-tyrosines [40].

*Aging.* The decreased functional activity of the aging brain is probably due to a slowing down in the rate of its metabolism, this being the result of a progressive diminution in circulatory rate [37]. This view is supported by the

fact that there is associated with old age some degree of cerebral arteriosclerosis with progressive increase in cerebral vascular resistance. As Kety [37] points out, however, an observation not easily reconciled with this hypothesis is that in mental states that have been affected by acute anoxia or hypotension there is little evidence of a significant decrease in cerebral oxygen consumption. Values of rates of cerebral oxygen uptake may, however, be insufficient to indicate changed metabolic events in parts of the central nervous system. It is now well known that a marked change in cell metabolism may occur without a concomitant drop in the rate of oxygen consumption; certain agents that "uncouple" phosphorylations from oxidations may even bring about enhanced rates of oxygen consumption. Conceivably, therefore, a change in the functional activity of the nerve cell can take place without an immediate fall in its respiratory activity. In subjects of seventy-six years average age, suffering from senile psychoses, a lower than normal rate of blood flow and an 18 per cent drop in the normal rate of oxygen consumption have been found [32] but perhaps "the restricted cerebral circulation and increased vascular resistance could follow rather than cause the decreased metabolism" [37].

*Nutritional Deficiencies.* *Pellagra:* Psychotic symptoms associated with pellagra are relieved by administration of nicotinic acid or its amide [41] although there is but scant evidence that uncomplicated nicotinic acid deficiency leads to injury in the nervous system [42]. Lehmann [41] points out that the therapeutic effects of nicotinic acid administration in psychotic states characterized by stupor, lethargy, coma or confusion are not necessarily due to the correction of a nicotinic acid deficiency; possibly the large doses given have other effects on the nervous system.

*Beri-beri.* Patients deprived of thiamine show a variety of cerebral changes, including depression, anxiety, irritability and loss of memory. If the deprivation is severe, serious disorders of the nervous system occur which may be accompanied by the peripheral neuropathy characteristic of beri-beri. In prolonged deprivation of thiamine, neurological changes are the most prominent clinical features; an acute deficiency would be more accurately described as producing personality changes [42]. These symptoms are relieved by the administration of thiamine. There seems to be little doubt from the clinical and biochemical evidence that the cerebral abnor-

malities due to thiamine deficiency are linked with the well known fact that diphosphothiamine is required for pyruvic acid metabolism in the nervous system. This phenomenon was among the earliest to indicate the importance of carbohydrate metabolism for the normal functioning of the central nervous system. It is for this among other reasons that consideration of the enzymes involved in the familiar Embden-Meyerhof scheme for glucose breakdown to pyruvic acid and those involved in the oxidation of pyruvic acid by the citric acid cycle of operations must receive attention in studies of cerebral dysfunctions. The alternate glucose oxidation pathway, known nowadays as the "pentose phosphate cycle" is beginning to attract attention as a brain mechanism and may possibly be implicated in neurological disorders. It is well to realize that thiamine (as the pyrophosphate) is a co-factor for transketolase [43] which is involved in the pentose phosphate cycle. If so, the deprivation of the brain of thiamine may affect the "pentose phosphate cycle" as well as the metabolism of pyruvic acid itself.

Both in patients with beri-beri and in dogs with experimentally induced thiamine deficiency the concentrations of pyruvic and lactic acids in the blood are found to vary directly with the severity of the disease. The sites for pyruvic acid production seem to be the peripheral nerves, cord, various parts of the brain stem, cerebellum and cerebral hemispheres. Correlation between degenerative changes in the central nervous system, clinical symptoms and biochemical abnormalities occurs not only in man but in the dog and in the pigeon [42].

Wernicke's encephalopathy, characterized by clouding of consciousness, ataxia and ophthalmoplegia, with foci of nuclear degeneration and hemorrhage in the midbrain and hypothalamic region of the brain stem, responds to treatment with thiamine. The disease is regarded by some as a cerebral form of beri-beri [44] but it can occur under circumstances in which there is no evidence of dietary inadequacy.

Nutritional factors appear to play an etiological role in alcoholic polyneuritis, in the polyneuritis of certain gastrointestinal disorders and in the polyneuritis of pregnancy. Usually treatment with thiamine and a nutritious diet relieves these conditions, but in human polyneuritis "no reversible biochemical disturbance seems to explain all the clinical phenomena" [42].

Lathyrism is an example of a crippling neuro-

logical disturbance due to special dietary conditions, the consumption of certain pulses, and occurs in India and other parts of Asia. The responsible toxic factor presumably induces biochemical abnormalities in the nervous system.

Treatment of flour with nitrogen trichloride, a process used in the "improvement" of flour, produces methionine sulfoximine [45] which is responsible for canine hysteria and neurological disorders in certain animals (monkeys, cats, ferrets but not rats, chickens or guinea pigs). The symptoms, as indicated by electroencephalograms, resemble those of human epilepsy. Methionine sulfoximine inhibits glutamine synthesis in brain preparations and relieves the inhibition induced by ammonium ions on acetylcholine synthesis in the brain cell [46]. Possibly the interference of methionine sulfoximine with glutamine metabolism is linked with its ability to produce neurological disorders.

*Cerebral Dysfunction and Renal Failure.* The uremic patient commonly shows meningeal irritations and cerebral signs of unsteadiness, change in gait and nystagmus. The cause of the neurological disturbances is unknown but it has been found that with external hemodialysis complete reversal of mental and physical conditions occurs. The extent of the reversal is variable and is independent of the removal of urea [47]. It is suggested that there is a relationship between the uremic syndrome and protein catabolism.

*Cerebral Dysfunction and Hepatic Coma.* Clinically, hepatic coma is a condition of the brain leading to mental confusion, drowsiness, stupor and coma [48]. It is possible to induce hepatic coma by feeding ammonium salts or proteins to patients with liver disease. Ammonium ion concentrations in arterial and venous blood are increased in hepatic coma but not in liver disease without neurological manifestations [48]. The most effective treatment involves complete withdrawal of protein from the diet with antibiotic treatment to affect bacteria in the gastrointestinal tract, with later gradual increase of proteins to the point of toleration. The data offer support for the hypothesis that ammonia is an important agent in the development of hepatic coma [48] although it may not be the only one. In this connection it should be noted that ammonium ions inhibit the aerobic synthesis of acetylcholine in the brain, probably by increasing the rate of synthesis of glutamine and thereby diminishing the available adenosine triphos-

phate needed for acetylcholine formation [46] and possibly other functional activities of the nerve cell.

*Bilirubin Encephalopathy.* The normal pathway of bilirubin detoxication is by conjugation with glucuronic acid followed by excretion of the glucuronide in the bile. It is possible, however, that the rate of bilirubin production may exceed that of its removal, as in erythroblastosis fetalis, or when the liver conjugates the bilirubin at a rate much lower than normal, as for example in infancy. Zetterström and Ernster [50] point out that in such cases, regardless of the etiology of the hyperbilirubinemia, a syndrome of severe brain damage may develop, called kernicterus or bilirubin encephalopathy. Using isolated mitochondria these authors have shown that bilirubin interferes with the process of oxidative phosphorylation. This occurs with concentrations of bilirubin less than those required to depress the rate of oxygen consumption. In this respect, bilirubin resembles a variety of narcotics.

Recent evidence [57] has indicated that the increase in serum bilirubin in congenital non-hemolytic jaundice is due to a failure of the enzymes normally present in the liver microsomes to bring about the conjugation of bilirubin with glucuronic acid by way of the coenzyme uridine-diphosphoglucuronic acid.

It seems possible that the brain damage may result from the increased concentration of bilirubin which presumably has the same effect on brain mitochondria as it does on liver mitochondria. It is suggested that the increased levels reached in the newborn may result from the inability of the blood-brain barrier in the immature infant to prevent the entry and eventual deposition of bilirubin in the cerebral tissue.

It has been pointed out, however [49], that in infants with hyperbilirubinemia there is some degree of hepatic dysfunction. It is suggested that there is a hyperammonemia that results in energy impairment in the brain. Consequent failure to maintain impermeability of the nerve cell membrane leads to staining by bilirubin and to irreversible damage [49].

*Hormonal Disturbances.* Cerebral dysfunction often accompanies hormonal disturbances, as in diseases of the thyroid, adrenals and pancreas. Hypopituitarism and adult eunuchism are characterized by a sluggish rate of cerebral oxygen consumption [57]. The data seem to demonstrate hormonal, and specifically steroidal, control of cerebral metabolism in man and rat.

Anesthesia is reported to follow the intramuscular injection of 11-hydroxy-androsterone in man [52] and it is known that certain steroids produce anesthesia in experimental animals [53]. Pincus and Hoagland [54] showed that administration of delta-5-pregnenolone to human subjects gives rise to a raising of the threshold to fatigue in psychomotor tests. Steroid administration is well known to result in a variety of symptoms, euphoria, exhilaration, depression, well being and convulsions. Gordon et al. [55] have shown that the steroids having anesthetic potencies also affect brain respiratory activities, and indeed viadril® (3:20-diketopregnane-21-ol) greatly inhibits brain mitochondrial respiration [56]. There seems to be little doubt that the steroid hormones may exert direct effects on the central nervous system by interference or involvement with metabolic events taking place there.

*Cerebral Dysfunction in Ischemia and with High Oxygen Tension.* During ischemia and hypoxia of the brain, which may cause functional paralysis followed by irreversible damage due to lack of respiratory energy, the first mental disturbances and alterations of the encephalogram coincide with the diminution of total cerebral oxygen consumption [58]. Biochemical changes quickly take place after interruption of blood flow to the brain; brain phosphocreatine disappears and ammonia content is increased. After an ischemia of about ten minutes the adenosine triphosphate content is about 15 per cent of the control. The functions of the brain are completely paralyzed but "the energy supply is still sufficient for structural requirements" [58].

High oxygen tension, as shown originally by Bert, is highly toxic to the nervous system, inducing convulsions. Bert considered the convulsions to be central in origin. High oxygen tensions also inhibit the respiratory activity of excised brain, the pyruvic oxidase system being particularly vulnerable [59]. Possibly the thiol enzymes in general are sensitive to high oxygen tensions, which may therefore be regarded as a specific enzyme poison. Protective effects on the brain against the action of high oxygen tensions may be obtained with various cations such as manganese, cobalt, magnesium or calcium, but these substances will not reverse the effects of high oxygen tension once they have developed.

*Lead Poisoning.* Many industrial poisons have generalized effects which may include effects

on the nervous system. However, the consequences of poisoning by lead seem to be rather more directly associated with the brain itself since they include epileptiform convulsions, paralysis, headache, delirium and melancholic mania. Many explanations have been offered, such as cerebral arteritis, arteriosclerosis or anemia; a direct action of lead on cortical cells; meningeal lesions or even indirect effects from kidney dysfunction or disturbed porphyrin metabolism. Although localized lesions such as minute hemorrhages and cellular infiltrations have been found in the brains of patients who have died of lead encephalopathy it is possible to attribute the symptoms to the increased intracranial tension due to intense cerebral oedema. This is particularly true when the effects of lead on the early morphogenesis of the chick are studied since effects may be observed which range from small herniation of the meninges to hydrocephalus. The basic biochemical disturbance produced by the presence of lead and its organic derivations such as lead tetraethyl remains unknown. It is possible, however, that new results [60] indicating that lead tetraethyl at low concentrations interferes with the transport of amino acids into the brain may throw light on the biochemical nature of the cerebral dysfunction. Tin tetraethyl, which also exerts neurological effects *in vivo*, behaves similarly to lead tetraethyl although it is quantitatively not so effective. Triethyl tin, which seems to affect the central nervous system as the main site of action in the body, inhibits brain mitochondrial oxidative phosphorylations and brain cortex respiration [61].

*Narcotics, Anesthetics and Tranquilisers.* It is now well known [62] that narcotics, with the exception of the alkaloid group containing morphine and allied substances, have the power of inhibiting at low concentrations the respiration of isolated brain tissue in the presence of glucose or pyruvate especially if this is examined in the form of intact slices or as brain mitochondria. This conclusion applies to local anesthetics, to chlorpromazine and to the steroid narcotics. There is, in fact, a close correlation between hypnotic activity and respiratory inhibition among narcotics and anesthetics of different chemical types. The high sensitivity to narcotics and anesthetics of glucose oxidation in the brain is a striking feature of narcotic action *in vitro*. Such observations have made it seem possible that the interference with brain

function accomplished by narcotics and allied substances is related to changed metabolic events in the nerve cell as a result of the presence of the drug. The concentrations of narcotics required to accomplish inhibitory effects on neuronal respiratory metabolism are, however, so large compared with those required to induce narcosis that the affected reactions have been thought to have no relation to the narcotic state. Further work, however, has made it clear that narcotics, at low pharmacological active concentrations, exhibit two phenomena: (1) the uncoupling of phosphorylation from oxidative processes [63], which is followed by a depressing effect on total oxygen consumption, and (2) the suppression of neuronal respiration that has been stimulated either by application of electrical pulses [64] or by exposure to a potassium ion concentration approximately equal to that in the neurone itself [65]. The high sensitivity of stimulated nerve respiration to chloretone, which was noted by Bronk and Brink in 1951 [66], makes the mechanism of potassium stimulation of glucose respiration of brain of importance in connection with brain function. Apparently the effect of the presence of potassium ions is to stimulate a rate limiting step in or associated with the citric acid cycle operating in brain respiration, but the precise nature of this step and its site in the nerve cell are at present unknown, although the neuronal or perhaps the mitochondrial membrane is implicated [67].

It is of interest that the stimulation of brain slice respiration due to electrical impulses takes place with the same substrates (glucose, pyruvate, lactate) which permit responses to the action of potassium ions. All the evidence points in fact to the similarity in many respects of the biochemical effects of electrical stimulation of the brain slice with those of potassium ions at 0.1 molar concentration. Brain homogenates or minces are, as is well known, unresponsive to either forms of activation. The present evidence would indicate that narcotics, anesthetics, a tranquiliser such as chlorpromazine [68], aliphatic alcohols or aliphatic aldehydes [69] exercise a large suppressing effect on the respiration of the activated or stimulated nerve cell, this stimulated respiration being brought about by the operation of the citric acid cycle. Presumably in the conscious animal such stimulation operates by the action of sensory impulses, and high sensitivity to narcotics of the metabolic

activity of the stimulated neurone ensues. This concept of an activity metabolism is by no means new [70].

Amytal is a highly effective inhibitor of oxidation of reduced diphosphopyridine nucleotide (DPHN) and the associated phosphorylations [71], a result that is in accordance with earlier conclusions on the site of action of narcotics in the nerve cell [62]. The known interference of narcotics with the oxidative synthesis of adenosine triphosphate in the nerve cell is reflected by their inhibitory effects on acetylcholine synthesis. Presumably they should interfere with a variety of metabolic processes dependent on oxidative formation of ATP. Rossiter and his colleagues [72] have shown that low concentrations of narcotics (chloretone, nembutal) exercise large inhibitions of  $P^{32}$  incorporation (from phosphate) into phosphoproteins and organic phosphorus compounds in respiring cat brain slices in the presence of glucose.

It is important to emphasize that the effects of narcotics on the metabolism of the nerve cell do not necessarily imply that all nerve cells in the brain are equally affected during narcosis or that a depression of total brain or body respiration should ensue. As a corollary, it does not follow from only the fact that there is a fall in brain respiration *in vivo* during narcotic states that respiratory depression in the nerve cell is a cause of narcosis [83].

It is pertinent to add that the stimulatory effect of potassium ions on aerobic nerve metabolism is greatly decreased in infant brain [73]. The response to potassium increases from the time of birth to forty days of age. The inhibitory effect of malonate on brain respiration, which is exercised on the citric acid cycle, also increases with age during the first ten days of postnatal life [74]. In accordance with the conclusions that have been mentioned, narcotics such as pentobarbital and alcohol exercise a larger percentage depression of respiration in the brain of the adult rat than in the young rat [75].

*Effects of Amines.* Amines derived from tyrosine, tryptophane and leucine have effects on brain respiration similar to those of the narcotics [76]. It has been pointed out that amine oxidase, the enzyme responsible for amine oxidations in brain, is inhibited competitively by amine analogues, such as amphetamine [77], and that the relative stimulatory effects of amphetamine and its derivatives on the central

nervous system bear a parallelism to their effects on amine oxidase, a suggestion supported by the later work of Oota [78]. The amines, on oxidation in the brain, give rise to the corresponding aldehydes which have high toxicity to brain respiration mechanisms [69,77], this toxicity being much greater than that due to the parent amines. The aldehyde undergoes a dismutation to the corresponding alcohol and acid in the brain [76], so that it is evident that an aldehyde mutase plays a role in the dynamics of brain chemistry. No attempt has been made yet to explore its possible role in brain function or cerebral dysfunction. The relatively recent discoveries of noradrenaline and hydroxytryptamine (serotonin) have focussed interest anew on the physiological significance of amine oxidase in brain, for it has been shown by Brodie et al. [79] that the amine oxidase inhibitors, ephedrine and iproniazid, suppress the metabolism of the amines mentioned and iproniazid administration to rabbits increases their levels in the brain stem. The effects of indole derivatives on brain metabolism are demonstrated not only by the results of early experiments with tryptamine, indole and skatole [76], but by the new studies with the tranquiliser reserpine and the psychotomimetic drug lysergic acid diethylamide (LSD) which, like serotonin, contain the indole nucleus. Wooley and Shaw [80] have indeed suggested that LSD produces behavioural abnormalities by interfering with the physiological action of serotonin in the brain. Reserpine apparently frees both noradrenaline and serotonin from their depots. After administration of reserpine to rabbits, the brain levels of these amines decline as they are released and destroyed by amine oxidase [79]. At present a very active interest is being taken in the enzymes concerned with the formation and destruction of products derived from adrenaline and tryptamine because of their psychopharmacological effects [81]. Weil-Walherbe has suggested in fact that a connection exists between the level of mental activity and the concentration of adrenaline in the plasma [82].

A few further words may be written about the effects of administration of metabolite analogues on cerebral dysfunction. It is reported [84] that the administration of 3-acetylpyridine, an analogue of nicotinamide, leads to severe lesions in the hypothalamus. The development of neural abnormalities by acetylpyridine may be prevented by administration of nicotinamide but

not of nicotinic acid. Apparently the phenomenon is due to competition of acetylpyridine and nicotinamide for incorporation into DPN by the controlling enzyme, DPN-ase. It is concluded that the toxicity of acetylpyridine is due to an exchange reaction *in vivo* forming the acetylpyridine analogue of DPN. Another nicotinamide analogue, 6-aminonicotinamide, also affects the nervous system, particularly the brain of developing chick embryo [85]. An analogue of ephedrine, deoxyephedrine, restores to normal behaviour animals that have become greatly depressed and immobile through reserpine administration [86]. Apparently the ephedrine analogues can substitute effectively for the catecholamines that have become depleted due to the action of reserpine.

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# Clinico-pathologic Conference

## Total Body Radiation in Acute Monocytic Leukemia

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A THIRTY-FOUR year old white housewife (B. W.) entered Barnes Hospital for the eighth time on December 2, 1957, with acute monocytic leukemia. She died on December 24, 1957.

The patient's first five hospitalizations in this medical center, from 1953 to 1956, had been at the St. Louis Maternity Hospital. These had been for threatened abortion necessitating dilatation and curettage of the uterus, delivery of a premature infant, threatened abortion, and incomplete abortion. The hemograms had always been within normal limits. Two of three urinalyses had demonstrated proteinuria.

The patient was admitted to Barnes Hospital on June 22, 1957 for the sixth time, complaining of irregular menses for one year. She reported increasingly heavy menstrual flow with clots and premenstrual spotting for four to five months, bleeding of the gums for six weeks, and easy bruising and spontaneous ecchymoses for one month. There had been a weight loss of 5 to 10 pounds in the month prior to this admission, but no anorexia. She had noted no chills, fever, night sweats, or lymph node enlargement.

Physical examination revealed a temperature of 37.4°C.; blood pressure, 120/80 mm. Hg; pulse, 88. The patient was a well developed, thin, rather apprehensive white woman, alert, cooperative and in no acute distress. Ecchymoses were present on the legs and gums. No petechiae were seen on the skin or mucous membranes. There was no lymph node enlargement. The chest was clear to percussion and auscultation, and examination of the heart revealed no abnormalities. No masses or organs were palpated in the abdomen.

The hemoglobin was 8.9 gm./100 ml.; the red

blood cell count, 2.21 million/cu. mm.; and the microhematocrit, 24 per cent. The platelet count was 34,000/cu. mm. The reticulocyte count was 4.8 per cent. The white blood cell count was 1,600/cu. mm.; examination of the peripheral blood film revealed 28 per cent polymorphonuclear leukocytes, 2 per cent myelocytes "C," 60 per cent lymphocytes, and 10 per cent monocytes, of which 4 were young forms. The urine specific gravity was 1.026 and the reaction was 6.5. There was 4 plus protein in the initial specimen but none in a repeat specimen, and the reaction for sugar was negative. Only an occasional white blood cell was seen per high power field in the centrifuged sediment. The total serum protein was 7.2 gm./100 ml. with 5.2 gm. albumin and 2.0 gm. globulin. An L.E. preparation was negative.

Sternal bone marrow was very cellular marrow and diffusely infiltrated with immature cells of the monocytic series, including monoblasts and young monocytes. The erythroid cells were numerous in some areas and scanty in others; there appeared to be more erythroid activity in the marrow than the differential count indicated. The megakaryocytes were decreased, although some were present. The per cent distribution of nucleated cells in the bone marrow was as follows: segmented neutrophils, 1; band neutrophils, 1; metamyelocytes, 2; C-myelocytes, 4; eosinophils, 3; lymphocytes, 22; monocytes, 8; monoblasts and young monocytes, 55; reticulum cells, 4; 19 normoblasts and 1 late erythroblast per 100 white cells.

The patient was treated with 6-mercaptopurine, 150 mg. daily, and prednisone, 40 mg. daily. She received 3 units of blood by transfusion; and was discharged in August, 1957.

The patient was admitted to Barnes Hospital for the seventh time on November 13, 1957. She was discharged on November 25, 1957.

In the interval between hospitalizations the patient did moderately well. Two weeks following her discharge the patient returned with a maculopapular rash over the entire body; this was thought to be a reaction to doriden® (glutethimide). The administration of this drug was discontinued and chloral hydrate was substituted. Administration of 6-mercaptopurine was discontinued the following day. Within one week the rash had disappeared. Two months following the patient's discharge, furuncles developed in both axillae. These responded slowly to hot soaks, penicillin administered intramuscularly, and tetracycline administered orally. In the four months between admissions the patient received seven blood transfusions. The dose of prednisone was gradually decreased to 10 mg. daily. There was a gradual decline in the patient's strength. Four days prior to this admission the patient had chills, fever, headache and myalgia. A cough developed and the patient produced small amounts of sputum.

Physical examination revealed a temperature of 38°C.; pulse, 100; and respirations, 20. The patient appeared acutely ill. Slightly reduced fremitus was detected in the right axilla. No rales were present in the chest. The liver was palpable 4 cm. below the right costal margin and the spleen tip was palpable at the right costal margin.

The hemoglobin was 7.8 gm. per cent; white blood cell count, 1,250 with 28 polymorphonuclear leukocytes and 72 lymphocytes. The urinalysis showed 1 plus protein, and 6 to 8 blood cells per high power field in the centrifuged sediment. The non-protein nitrogen was 29 mg./100 ml., and the fasting blood sugar 149 mg./100 ml. A roentgenogram of the chest showed pneumonia of the upper right lobe with patchy densities in the lower right, lower left, and upper lobes. Right hilar lymph node enlargement was present. A sputum culture produced a heavy growth of alpha hemolytic streptococci and paracolon bacilli.

The patient was maintained on prednisone therapy, received streptomycin and penicillin intramuscularly, and subsequently tetracycline, penicillin, and benemid® orally. Her course was febrile for ten days. She was essentially afebrile for the last few days of hospitalization. There was little change in the appearance of the chest

roentgenogram on the day of discharge. However, for psychological reasons the patient was permitted to go home, taking prednisone, 20 mg. a day, penicillin, benemid, tetracycline and demerol® orally as needed. She received 2 units of blood during her hospitalization. Prior to discharge a blood sugar determination obtained two hours postprandially was 137 mg. per cent.

The patient's eighth admission to Barnes Hospital was from December 2, 1957 through December 24, 1957.

In the interval between admissions, the patient remained weak. Herpetic lesions developed on her upper lips and did not heal. She received one blood transfusion one week prior to this admission. Three days later a fine papular non-pruritic rash developed, primarily on the trunk. The rash increased with coalescence of papules and the development of petechiae and ecchymoses, especially over the abdomen.

Physical examination showed a temperature of 37.2°C.; pulse, 96; respirations, 16; and blood pressure, 110/80 mm. Hg. The patient appeared as a well developed, well nourished white woman in no acute distress. An herpetic blister extended from the left nostril to the mucous membrane of the upper lip; it protruded 1 cm. and was covered with a black crust. A second herpetic lesion of the lower lip was similar in appearance. The patient had a productive cough. Examination of the lungs and of the heart was within normal limits. The liver was easily palpable 5 cm. below the right costal margin, smooth and non-tender. The spleen was easily palpable just under the left costal margin. The bowel sounds were active. Deep tendon reflexes were hyperactive. A maculopapular rash was present over the trunk. Occasional petechiae were noted in some of the papules, and a few small ecchymoses on the abdomen. The extremities and scalp were not involved with the rash. No enlarged lymph nodes were detected.

The hemoglobin was 9.8 gm. per cent; the white blood cell count was 16,050 with 4 eosinophils, 16 polymorphonuclear leukocytes, 68 lymphocytes, 4 monocytes, and 8 monoblasts. The reticulocyte count was 1.8 per cent, and the platelet count 8,000. The urinalysis showed a specific gravity of 1.025 and a pH of 4.5. Protein and sugar were not present. An occasional white blood cell was found in the centrifuged sediment. The stool was negative to the benzidine reaction. The non-protein nitrogen was 12 mg. per cent, and the serum uric acid

TABLE I  
SERIAL HEMATOLOGIC AND CHEMICAL DATA

Determination	December										
	3	5	7	9	11	13	15	17	19	21	23
Hemoglobin (gm./100 cc.)	10.1	9.4	8.2	7.5	7.5	6.2	...	7.1	7.0	5.7	5.3
Hematocrit (%)	30	27	25	23	22	18	28	22	22	20	18
White blood count (per cu. mm.)	1600	600	800	200	300	600	300	100	200	200	300
Neutrophils (%)	...	17	...	...	11	...	20	2	...	...	2
Lymphocytes (%)	...	68	...	...	77	...	54	69	...	...	93
Monocytes (%)	...	3	...	...	9	...	12	16	...	...	...
Monoblasts (%)	...	8	...	...	2	...	10	7	...	...	...
Plasma cells (%)	...	...	...	...	...	...	...	4	...	...	5
Reticulum cells (%)	...	...	...	...	...	...	...	3	...	...	...
Platelets (X 100)	...	50	...	...	60	...	5	...	...	...	...
Bilirubin direct/indirect (mg./100 cc.)	...	.8	...	...	...	...	...	7.8	...	.8/.6	...
Cephalin flocculation	...	...	...	...	0	...	...	3+	...	...	...
Thymol turbidity	...	...	...	...	9.9	...	...	26	...	...	...

NOTE: Total body radiation on 12/4/58; marrow transfusion on 12/5/58.

2.1 mg./100 ml. Serum electrolytes were within the normal range. The serum bilirubin was less than 0.8 mg./100 ml. Total serum proteins were 6.6 gm./100 ml.; albumin, 4.3 gm./100 ml.; and globulin, 2.3 gm./100 ml. Serial hematological and chemical determinations are recorded in Table I.

On the second hospital day the patient received 400 r of whole body radiation, administered by Betatron in four hours and thirty-five minutes. During this period of radiation exposure the patient vomited seven times and was extremely tired and nauseated.

The patient's blood types and groups were as follows: type B, Rh positive, (C/D/e/c), Duffy and Kell negative, MN. On the third hospital day bone marrow was obtained from a donor who was type B Rh positive, (C/D/e/c), Duffy positive, Kell negative and MN. After appropriate preparation, the patient was given a transfusion of 110 ml. of bone marrow and blood, aspirated from the sternum and both iliac crests of the donor. It was estimated that she received 2.7 billion nucleated cells in this manner.

All procedures including vena punctures were performed with aseptic technic. On the day following the bone marrow transfusion the patient felt improved and stated that she had not experienced nausea since twelve hours following the roentgen radiation. During the first nine days following the bone marrow transfusion she felt progressively better. The rash on her

arms and the herpetic lesions subsided slightly. The liver decreased in size by an estimated 1 to 2 cm. The spleen was no longer palpable. During this time, administration of prednisone, 20 mg./day and sulfasuxidine, 2 gm./day was continued.

On the tenth day following total body radiation, the patient had a mild headache in the morning and slight bleeding around the herpetic lesions on the upper lip. A 1 by 1.5 cm. ecchymosis was noted in the right buccal mucosa. At 8 P.M. she experienced a chill followed by an elevation of her temperature to 38.7°C. There were no localized complaints nor were any abnormalities noted on physical examination. Culture made of the urine at this time produced a heavy growth of proteus organisms. A blood culture subsequently grew out an alpha-hemolytic streptococcus in the thioglycolate broth only. A throat culture produced a moderate growth of alpha-hemolytic streptococci, a moderate growth of paracolon bacilli, and a few white staphylococci. Tetracycline was added to the therapeutic regimen. During the ensuing four days, the patient's temperature rose to between 39.7° and 40.5°C. daily. At about this time, her stools were persistently positive to the benzidine test but remained negative to the guaiac test. Vaginal bleeding commenced and was associated with gushes of blood. The patient was followed closely and blood was replaced by transfusion. At this time she noted nausea and

vomiting. "Coffee ground" material was vomited several times but discarded before it could be examined for the presence of blood. She received thorazine® for her nausea and blood transfusions were continued, being necessary to maintain the blood pressure above hypotensive levels. The dose of prednisone was doubled. A bone marrow aspiration obtained on the fifteenth day following total body radiation revealed a very hypocellular marrow. One small clump of marrow contained a few granulocytic and nucleated cells. Many immature cells were seen on another preparation and appeared to be young monocytes or monoblasts. No megakaryocytes were observed.

Daily urinalyses obtained on the fifteenth to nineteenth days following total body radiation showed 4 plus glycosuria. On the sixteenth day following radiation, ecchymoses of the eyelids and conjunctivas as well as purpuric spots and rare petechiae were noted on the patient's skin. At this time a carbuncle was first noted to be developing in the right axilla.

A soybean lipoprotein extract was administered intravenously as a platelet substitute in an effort to control the hemorrhagic manifestations. This extract appeared to diminish the periorbital and vaginal bleeding, but no improvement in the patient's prothrombin consumption could be demonstrated. On the eighteenth day following total body radiation the patient once again became afebrile. Vaginal bleeding increased and the stools became guaiac positive for the first time. It was thought that gastrointestinal hemorrhage accounted for a significant portion of the fall in the hematocrit. A culture of the abscess in the right axilla produced a heavy growth of pyocyanus. The patient's course was that of progressive deterioration with spiking fever, gastrointestinal hemorrhage as evidenced by hematemesis, bloody diarrhea, and abdominal distention. Continuous transfusion was necessary to maintain the patient's blood pressure. On the twentieth hospital day, she vomited blood and appeared to have aspirated at that time. The pulse and heart beat were no longer detectable and she died. The patient received a total of 22 units of blood during this hospitalization.

#### CLINICAL DISCUSSION

DR. EDWARD REINHARD: There has been a recent surge of interest in the use of bone marrow transplantation procedures for the treatment of

acute leukemia. Hardly a day passes without some physician, patient, or relative of a patient telephoning to inquire whether or not we are equipped to treat some patient, desperately ill with acute leukemia, by *bone marrow transplantation*. A discussion of this subject is therefore extremely timely. Today we will discuss the progress which has been made in this field, emphasize the tremendous problems, and the questions which remain unanswered. This patient had an unequivocal diagnosis of acute leukemia which we classified as monoblastic leukemia. The diagnosis was first established in June 1957. At that time she gave a one year history of increasingly heavy menstrual flow, with premenstrual spotting for four or five months before admission to the hospital. She had bleeding of the gums for six weeks as well as easy bruising and spontaneous ecchymoses for one month. She had lost 5 or 10 pounds in the month before admission. I believe that these manifestations beginning a full year prior to the time the diagnosis was established were probably related to her leukemia. From June 1957 to December 1957 an attempt was made to keep the disease under some semblance of control by conventional therapy with 6-mercaptopurine and with steroids. Dr. Brittingham, would you please comment on this patient's response to 6-mercaptopurine therapy? I am particularly interested in the problem of dosage regulation in a patient whose original white blood cell count was only 1,600 and whose platelet count was fluctuating between 5,000 and 35,000 before therapy was started.

DR. THOMAS BRITTINGHAM: Dr. Reinhard, there is absolutely no evidence that this lady responded to 6-mercaptopurine therapy. In the usual patient with leukemia who has a normal or elevated total leukocyte count, the level of the white count is a very satisfactory guide for the response to therapy. In a patient such as this one, who presents with leukopenia, the problem is much more difficult. One must perform serial bone marrow examinations and then discontinue drug therapy when (1) the leukemic cells have largely disappeared from the bone marrow, (2) when the bone marrow becomes excessively hypoplastic, or (3) when the physician believes that an adequate trial has been given without benefit. This patient had six or seven bone marrow examinations during the course of her therapy.

DR. REINHARD: Dr. Moore, it is sometimes

stated that corticosteroid therapy is contraindicated in acute monocytic leukemia. Do you believe that such therapy should not have been given to this patient?

DR. CARL V. MOORE: There are unquestionably a few patients with either acute monocytic or acute myelocytic leukemia who seem to be made worse with corticosteroid therapy. The number of such patients, however, is certainly small and most people have observed beneficial results, at least in terms of an increased sense of well-being and diminution of hemorrhagic manifestations. I do not believe that corticosteroid therapy is contraindicated in acute monocytic leukemia.

DR. REINHARD: The two major problems in attempting to keep any patient with acute leukemia alive are control of hemorrhage and of infections. This patient had constant difficulty with ecchymoses and other bleeding manifestations. She also had recurrent infections during the last four months of her life: furuncles, subcutaneous abscesses, pneumonia, and herpetic lesions on her lips complicated by cellulitis. The pulmonary lesions are documented in the chest roentgenograms.

DR. SUMNER HOLTZ: The first film was taken in June 1957. The chest examination was entirely negative. There are no areas of infiltration in the lung and there are no abnormal hilar nodes. The second film taken in September 1957, again failed to show any mediastinal nodes but there was pneumonitis in the upper right, the lower right, the upper left and lower left lobes. Throughout the lung fields there was a suggestion of a faint nodularity. All films subsequently showed no further change.

DR. REINHARD: Ordinarily when any organ is transplanted from one person to another, the transplanted organ will survive for only a very short period of time, unless the two persons are identical twins. Dr. Chaplin, I wonder if you would review briefly the experimental work which has led to the concept that it is theoretically possible to transplant bone marrow successfully even when the donor and recipient are not identical twins?

DR. HUGH CHAPLIN: A great deal of experimental work lies behind this concept, and only some of the high points can be mentioned here. The work has been carried on with a wide variety of animals: mice, rats, dogs, monkeys and others, but the chief animal work has been in mice and rats. The pattern of the experiments

is roughly as follows:\* a group of animals are given a dose of radiation sufficient to cause 100 per cent of them to die, if untreated. Half of these are kept as controls, the other half are given intravenous infusions of bone marrow. The marrow has been obtained from various sources. In some instances bone marrow is aspirated from the animal itself just prior to radiation and given back to the animal after radiation—an *autologous* marrow transplant. The next step is to give bone marrow from the same strain of animal, an *isologous* transfusion. The next step is to give marrow from a different strain within the same species—an *homologous* transfusion. The widest step has been to obtain marrow from a different species altogether—a *heterologous* transfusion.

In the initial work in which marrow from the same animal or the same species was given, it was difficult to determine whether the protection observed was due to a humoral factor present in the transplant or to actual repopulation of the marrow by the transplanted cells. However, Ford† in England showed that when a mutant strain of mouse with a peculiar chromosome abnormality was used as a donor it was possible to show that these unusual chromosomes were present in the bone marrow of the recipient radiated mice many weeks after the marrow transfusion. This was some of the first evidence of actual repopulation by the transplanted marrow.

The most interesting work is that in which lethally radiated mice were given transplants of rat bone marrow. It was shown that the rat marrow actually survives and multiplies in the mouse. The white cells of the rat are alkaline phosphatase positive while those of mice are negative. The alkaline phosphatase positive white cells surviving in the radiated mouse were obviously those of the rat. The platelets have also been shown to be rat platelets by serological methods and the red cells have been shown to be rat red cells by a variety of methods. Employing anti-rat red cell agglutinating serum one can show that the mouse's marrow is populated by rat red cells that have been formed and are surviving in the new host environment 60 to 200

\* MAKINODAN, T. and ANDERSON, N. G. Physicochemical properties of circulating red blood cells of lethally x-radiated mice treated with rat bone marrow. *Blood*, 12: 984-992, 1957.

† FORD, C. E., HAMERTON, J. L., BARNES, D. W. H. and LOUITT, F. F. Cytological identification of radiation chimerae. *Nature* (London), 177: 452-454, 1956.

days following the transplant. Further, the mechanical fragility of rat red cells is very much less than that of mouse red cells; in the surviving mouse, the mechanical fragility is low, characteristic of rat red cells. In addition, the hemoglobin electrophoretic patterns are typical of rat hemoglobin which differs clearly from mouse hemoglobin. Between three and seven weeks after the transfusion of the heterologous bone marrow there is a marked immunologic reaction in the recipient animal. Some animals reject the graft at this time and die, but in others a complete tolerance to the rat cells apparently develops; some animals have survived well over a year, have continued to produce rat hematologic elements and apparently live well with them.

DR. REINHARD: When so-called bone marrow transplantation is carried out in human subjects, the marrow is given by intravenous injection. There is one obvious and vitally important difference, however, between blood transfusion and bone marrow transfusion. For a bone marrow transplantation to be successful, the donor cells must be viable and presumably they must be seeded in an organ that provides a suitable environment for their growth. They must retain the ability to proliferate and continue to multiply in the host. Do you think, Dr. Harrington, that a great majority of the intravenously injected nucleated marrow cells escape from the capillaries into the lung or other organs in which they may not be able to multiply, and only those cells which happen to escape into hematopoietic organs ultimately set up a new focus of marrow? Or, can marrow cells multiply in almost any organ? With these possibilities in mind, are there any data on the fate of transfused marrow cells?

DR. WILLIAM HARRINGTON: There is an abundance of data to indicate that bone marrow infused intravenously will ultimately localize in the recipient's bone marrow, and with this accomplished no extramedullary hematopoiesis is then evident. I am more attracted to your second theoretical possibility, however, namely that when necessary, bone marrow can remain viable almost anywhere. It may be pertinent to recall that in certain clinical disorders extramedullary hematopoiesis may be widespread. Therefore, although we know nothing about the mechanisms which usually limit blood cell production to the bone marrow, it does not seem likely that repopulation following marrow

transfusions is dependent merely on the chance landing in the bone marrow of an occasional cell which then takes up residence there, while those seeded in all other sites die.

DR. REINHARD: A number of patients with acute leukemia have now been given total body radiation followed by bone marrow transplantation. Two of the most active groups working in this field are Dr. Tocantins and his collaborators in Jefferson Medical College in Philadelphia and the group in Oak Ridge, Tennessee. As of March 18 of this year Dr. Tocantins had performed seventeen total body radiations for acute leukemia on sixteen patients. One patient had two courses the first being only 40 r and the second being 250 r, eight months later. This patient was the first one they treated with total body radiation and marrow transfusion; that is the reason for the initial very cautious dose. Dr. Harrington visited Dr. Tocantins' laboratory several months ago and discussed the work with him. Dr. Harrington also wrote recently to Dr. Tocantins and asked for an up to date informal progress report on his experiments which might be presented at this clinical pathological conference. Dr. Harrington, would you tell us very briefly about the experiences of the group in Philadelphia?

DR. HARRINGTON: Dr. Tocantins has had extensive experience in testing the feasibility of bone marrow transplantation in human subjects. As mentioned he has evaluated the procedure on sixteen patients. Fresh cell suspensions were employed with careful assessment of their viability. Since Dr. Tocantins believes that bone marrow stromal cells may be important primitive precursors, he has obtained whole ribs from normal volunteer subjects and removed the marrow in toto. This material has then been injected as soon as possible into his patients. Among the sixteen patients, there has been one six month remission in a case of monocytic leukemia; this patient is still doing well. In some other patients, therapy was probably inadequate; the minimum effective dose of total body radiation is probably larger than that given and the quantity of marrow required is probably 3 to 5 times the maximum of 5 to 20 billion nucleated cells employed to date. Three of five patients who died received either less radiation or marrow than is now thought necessary. Of the remaining patients some have had transitory improvement but Dr. Tocantins is unenthusiastic about their prognosis. He con-

cludes his letter by pointing out the extent of the problems remaining. After his experience over the past few years Dr. Tocantins suspects that one may have to give at least 600 r of total body radiation, i.e., at least an L.D.<sub>100</sub> dose, and administer at least 50 billion marrow cells obtained from excised bones.

DR. REINHARD: What is the L.D.<sub>50</sub> radiation dose for human beings?

DR. HARRINGTON: I would guess that it is somewhere in the neighborhood of 450 to 500 r. In experimental animals it has required at least an L.D.<sub>100</sub> dose to get the effects Dr. Chaplin mentioned.

DR. REINHARD: To my knowledge, no one to date has carried out this procedure using a Betatron as the means of administering total body radiation. In our patient Dr. Holtz gave the treatment. Obviously if you try to destroy all the leukemic cells in the marrow of all the bones of a leukemic patient, a reasonably homogeneous distribution of radiation to all the bones of the body is of paramount importance. Dr. Holtz, would you discuss the theoretical advantages of supervoltage radiation as compared to conventional radiation in this situation?

DR. HOLTZ: Basically, when x-rays are absorbed in the tissue, electrons are produced which then form ions to induce changes known as radiation effect. Conventional (orthovoltage) x-rays generated at 250 K.V. have a maximum effect at/or near the surface, the effects decreasing rapidly as the depths are reached. At the orthovoltage level there is a differential absorption, proportional to the fourth power of the atomic number of the absorbing element. Thus, bone being of higher atomic number absorbs considerably more x-ray than fat and muscle. This is the very basis of diagnostic roentgenology. Also, at orthovoltage levels, electrons scatter forward, sideward, and backward; this widens the beam and increases the integral dose. To improve upon these effects we used the Betatron. The Betatron is an instrument where electrons are injected in a doughnut-shaped tube suspended between two alternating charged electromagnets. These electrons gain momentum during one cycle, strike a platinum target and non-monochromatic high energy x-rays are emitted. This emission occurs 180 times a second with a peak energy of  $22\frac{1}{2}$  million electron volts and an average energy of 9 million electron volts. Because of the high energy levels the maximum effect of the Betatron occurs not at the surface

but 4 cm. below the surface level. It can be shown that at the surface level the 100 per cent dose has been reached with 250 K.V. equipment, where with the Betatron the 100 per cent level is reached 4 cm. deep to the surface thus giving a skin sparing effect. Also, at the Betatron energy level the absorption involves primarily the so-called Compton effect, which is directly proportional to the atomic number rather than to the fourth power. This means that there is a homogeneous absorption through fat, muscle, and bone which we wanted very much in this particular case.

If one determines the energy absorbed in ergs per gram of fat, muscle, and bone using a 250 K.V. and the Betatron, it is seen that with 250 K.V. there is a large increase in absorption in bone whereas with the Betatron there is rather homogeneous absorption between fat, muscle, and bone.

Using conventional x-ray, a film of a shoulder demonstrates fine detail of bone, soft tissue, ribs, and the aerated lung. A similar film taken with the Betatron reveals practically no bone, lung, or fat. This graphically demonstrates the near homogeneous absorption. Using conventional x-ray equipment the output of the machine is such that usually eight to twelve hours of actual treatment time is required. With the Betatron the treatment time is halved. The Betatron's electrons are of such magnitude that there is little scatter to the side or backward but primarily forward. This is of perhaps little importance here but in ordinary cancer therapy it greatly defines the beam and decreases the integral dose which is definitely related to so-called "radiation sickness." An actual x-ray film made in a phantom using conventional equipment and the Betatron demonstrates with orthovoltage that the surface is the most exposed portion of the film, with the Betatron there is no surface exposure to speak of and the maximum exposure occurs 4 cm. from the surface. Also, it can be seen that the side of the exposure with conventional orthovoltage therapy is fuzzy and poorly defined while with the Betatron it is straight and sharply defined.

DR. REINHARD: I wonder, Dr. Holtz, if you could tell us some of the technical problems involved in giving 400 r of total body radiation to a patient in this situation.

DR. HOLTZ: In using external radiation certain details must be considered. The size of the portal must be sufficient to cover the whole body.

Under ordinary treatment distances with the Betatron (up to 120 cm.), the largest port that is used is approximately 6 by 6 inches. By increasing the distance from the machine to the patient we can increase the area of the portal to completely cover the patient. In this particular case in order to keep the increased distance at a minimum it was convenient to have the patient double up in a knee-chest position while sitting since the roentgen exposure decreases as the patient is moved further from the source. Both of these follow the inverse square law—that is, that as the distance increases, the size of the port and area increases as the square of the distance and the roentgen output decreases. These can be calculated exactly. The distance that must be used from the patient to the machine is of such a magnitude that the output of the machine is very small and quite a long time is required to treat these patients. In the Betatron, an ionization chamber is placed near the exit of the photons and is standardized with the roentgen output at the 80 cm. distance. This registers on the control panel as a count every time 10 r are reached. By checking this recording against the time and against the measured quantity at the specific distance used, accurate output measurements are obtainable. However, constant monitoring is essential.

DR. REINHARD: You will recall that the patient continued to have monoblasts in the peripheral blood up until the time of death and a bone marrow aspirate on the fifteenth day following radiation appeared to be hypoplastic but still contained some monoblasts. It is assumed that blast cells and other early precursors of the blood cells are extraordinarily sensitive to radiation and it has always been thought that in acute leukemia, the leukemia tissues are extremely radiosensitive. Dr. Moore does it surprise you that blast cells continued to be present both in the blood and in the bone marrow?

DR. MOORE: Yes, but I think in all fairness it must be said that identification of these cells became extremely difficult. I never was absolutely convinced for instance that they were still leukemic monoblasts rather than reticulum cells but it seems to me that in order to be fully critical of what we were accomplishing the safest thing to do is to assume that they were leukemic monoblasts that had not been destroyed.

DR. REINHARD: I agree and think that highlights what Dr. Harrington stated. In order to destroy all the leukemic tissues, probably one

would have to use a substantially larger dose than was given here (perhaps the L.D.<sub>100</sub> dose of 600 r of total body radiation or even more).

Now let us consider certain technical problems in connection with giving the bone marrow transfusion. First of all the problem of obtaining marrow from the donor. Dr. Tocantins has obtained his marrow, as Dr. Harrington mentioned, from the surgically removed ribs obtained from the chest surgery service. We decided to obtain our marrow by multiple aspirations from a single donor. Dr. Chaplin, I wonder if you would comment on the problem of typing and cross-matching the donor and the recipient, particularly with reference to the sub-blood groups in this particular patient? How important do you think it is that the donor's and the recipient's blood be identical in all measurable respects, particularly with regard to the major and minor sub-groups.

DR. CHAPLIN: We are trying to avoid or minimize immunologic rejection of the donor marrow by the patient. Therefore, theoretically absolute compatibility in all systems would be the ideal. Unless identical twins are used, that is essentially impossible. Fortunately there is a difference between the antigenicity of the various blood group factors. The Rh antigens are relatively strong antigens. Within the Rh-system, D is the strongest, E and C are much less strong. D is thought to be 100 times as strong an antigen as C. A strong antigen is the Kell blood group antigen; it is most important that the Kell-negative recipient receive marrow from a Kell-negative donor. However, the MNS, P, Lutheran, Lewis and some of the other systems are relatively non-antigenic. One must do the best he can in avoiding the notoriously strong antigens. In this patient there was essentially good agreement with the donor's blood group antigens. The major difference was in the Duffy system (patient Fy<sup>a</sup> negative, donor Fy<sup>a</sup> positive) and Duffy is not a particularly strong antigen. I would like to point out that the frequency of transfusion of the patient prior to the transplant complicates the whole problem. For one thing the early transfusions may sensitize the patient to various blood group antigens before the transplant is made. Even more difficult is the fact that it is next to impossible to determine the patient's own red cell antigen pattern, when the patient's circulation is full of transfused cells from a variety of donors at the time one is trying to make this very important characterization.

DR. REINHARD: The donor finally selected was a volunteer chosen from the Barnes Hospital professional donor list. Ten cc. of material was aspirated from each of six different sites. Dr. Loeb, would you comment on the most suitable sites for such aspiration and the type of needle that might be most suitable?

DR. VIRGIL LOEB: There are a number of techniques for obtaining large quantities of marrow from donors. One can aspirate marrow from various sites in the same donor, as was done in this case, and inject the material intravenously. The quality of the marrow cells is probably not very different in the various bones but the technical difficulty will vary from one site to the next. A technique which was suggested by Dr. Howard Bierman to obtain marrow in large quantity is as follows: He used a needle which is very similar to the needle we used, the significant difference being that the opening of the needle was on the side rather than at the end of the shaft and consequently the marrow can be aspirated liberally by rotating the needle as suction is applied. In this way one can obtain 10 to 20 cc. of marrow with one aspiration. He uses the posterior iliac spine as a site for obtaining marrow; the volume of this space being much larger, of course, than that of the sternum. There are other ways of obtaining marrow. We have already referred to the use of single ribs. Approximately 1 to 4 billion marrow cells can be secured from a single rib which is easily available in the course of a thoracotomy. These ribs are cut into small sections, then split and the marrow contents removed. The material is agitated in a buffer, the fat removed and the cellular residue then injected intravenously through a fine mesh screen at the end of the syringe. Other methods include the use of fetal marrow from which approximately 1 billion cells can be obtained from the skeleton. Cadaver marrow has been used when the marrow is obtained within a few hours of death, pressed out of the cancellous bones and suspended in a buffer. A yield of 40 or 50 billion cells can be obtained from a cadaver fairly easily, and can be infused intravenously. A great deal of work is going on now in an attempt to store marrow by freezing in glycerol and with other techniques, but as Dr. Harrington already has mentioned there is no unanimity of opinion as to the efficacy of stored marrow versus marrow freely obtained. Of course the problem of blood type compatibility limits the availability of any "marrow bank."

DR. REINHARD: It was supposed on theoretical grounds that in injecting such material intravenously one might encounter such problems as embolization and micro infarcts. In order to minimize this danger, if there is a danger, various things are done to the aspirated material before it is injected. Dr. Lessner, would you discuss the preparation of the donor marrow for intravenous injection?

DR. HOWARD LESSNER: There is as yet no standardized method of preparing marrow. Some workers place the marrow in a culture medium and homogenize it in a pyrex homogenizer. However, the method we used was that of Dr. Thomas in Cooperstown. A syringe is used the end of which is cut off and a fine wire mesh fastened over it. The marrow is passed back and forth through this fine mesh, and the larger particles are removed, separating the clumps of cells as much as possible. Cells treated thus are morphologically normal. In the patient under discussion, we took the marrow, put it into a volume of lactate-Ringer's solution and pushed it through a fine wire mesh screen several times, taking out the larger particles and splitting up the cellular clumps.

DR. REINHARD: Dr. Moore, I wonder if you would compare this patient's postradiation course with the sequence of events which has been observed in persons who have been exposed to lethal doses of radiation as a result of atomic fission catastrophes?

DR. MOORE: Information about the acute radiation syndrome comes largely from the experience with the Japanese and Marshallese after exposure to atomic radiation and also from the ten scientists who were accidentally exposed to atomic explosions at Los Alamos. These several exposures differ in three important regards from the kind of exposure which our patient got here today. In the first place atomic explosions are accompanied by blasts and burns; in the second place the radiation consists of fast neutrons and hard gammas as well as x-rays; in the third place some of the chemical elements in the patients so exposed are converted to radioisotopes so that there is internal radiation as well. How significant the latter factor is we do not know. However, four different phases of the acute radiation syndrome have been observed under these circumstances. The first phase lasts for approximately twenty-four hours and consists of nausea, vomiting, prostration, and moderate fall in blood pressure. That is fol-

lowed within twenty-four to forty-eight hours by a feeling of well-being during which time the subjects are free of symptoms unless they were burned. The third phase then begins somewhere around five to ten days later. It is characterized by a rather sudden onset of high fever, a pronounced weight loss and prominent gastrointestinal symptoms. In some cases, the third phase is associated with infection, as the white cell count drops, and with hemorrhagic manifestations. In the fourth phase there is either death or long convalescence. Clinically, our patient went through the first three of these phases very clearly and corresponded with them quite well.

From the hematologic point of view, in acute radiation syndrome there is usually an initial and marked leukocytosis, prompt lymphopenia, then gradually the development of leukopenia and thrombocytopenia. Our patient did not show those changes so clearly because of her associated leukemia. The bone marrow becomes aplastic or hypoplastic within a period of twenty-four to forty-eight hours. This hypoplasia lasts for a variable period of time; then in those who recover the marrow gradually returns to normal. I had a chance to examine the bone marrow of some of the physicists who were involved in experimental explosions; among those who recovered there was still marked aplasia several weeks later. Comparatively few other laboratory manifestations have been observed except terminally there tends to be a rise in the non-protein nitrogen and uric acid and a fall in the blood calcium and amino acid level.

DR. REINHARD: This patient had practically no platelets and severe hemorrhagic manifestations developed during the terminal phase of her illness. The bleeding was controlled for a considerable period of time by administration of a lipoprotein extract of soybeans. Dr. Lessner obtained this extract for us from Dr. Ralph Jones, University of Miami Medical School.

DR. LESSNER: There has been a tremendous interest during the last several years in preservation and storage of platelets as well as the substitution of other compounds which will correct the hemostatic defect in forms of cytopenias. At Children's Hospital in Boston, it has been shown that both *in vivo* and *in vitro* hemorrhagic tendencies of thrombocytopenia can be corrected with stored frozen platelets and even lyophilized platelets. This would imply that platelets need not be metabolically active to correct thrombo-

cytopenic difficulties. It is likely that some chemical component of platelets is active in coagulation. The substance is thought to be a phospholipid; chloroform extract of human brain is effective in correction of the hemostatic defect of platelet deficiency. Since the availability of human brain phospholipid is somewhat limited, a more fertile source was settled upon, namely, soybeans, which are very high in phospholipids. Bell, at the University of Pennsylvania, found that soybean phosphate was active in the thromboplastin regeneration test. Clinical trials with a crude soybean extract were made after appropriate animal toxicity studies. This compound was administered to several patients with thrombocytopenic bleeding; the bleeding tendency was corrected. The compound now available is still a rather crude soybean phospholipid. It has to be given intravenously and it is only effective during the course of the infusion. However, its availability is certainly an indication for further work with this compound, particularly with regard to the active fraction. We are also trying to make some type of repository compound which will be effective over a prolonged period.

DR. REINHARD: We all have the impression that this lipoprotein extract of soybean was at least temporarily effective in minimizing this patient's severe bleeding manifestations.

In conclusion I would like to say again that in acute leukemia death is usually due either to an overwhelming infection or to hemorrhage. An intracranial hemorrhage is present at post-mortem in a surprisingly large percentage of such patients.

My final diagnoses are: (1) Acute monocytic leukemia. (2) Disseminated infection attributable to agranulocytosis and disturbance of other normal mechanisms of defense against infection as a result of both the leukemia and the therapy. A likely organism would be the pyocyanous cultured from the abscess in the right axilla. (3) Massive hemorrhage, probably including an intracranial hemorrhage (on statistical basis).

#### PATHOLOGICAL DISCUSSION

DR. BERNABE B. BANSON: The skin appeared pale and contained multiple areas of petechiae and ecchymoses over the abdomen and thighs. Periorbital ecchymoses and conjunctival hemorrhages were also present. Serous fluid was present in the abdominal cavity (900 cc.), right

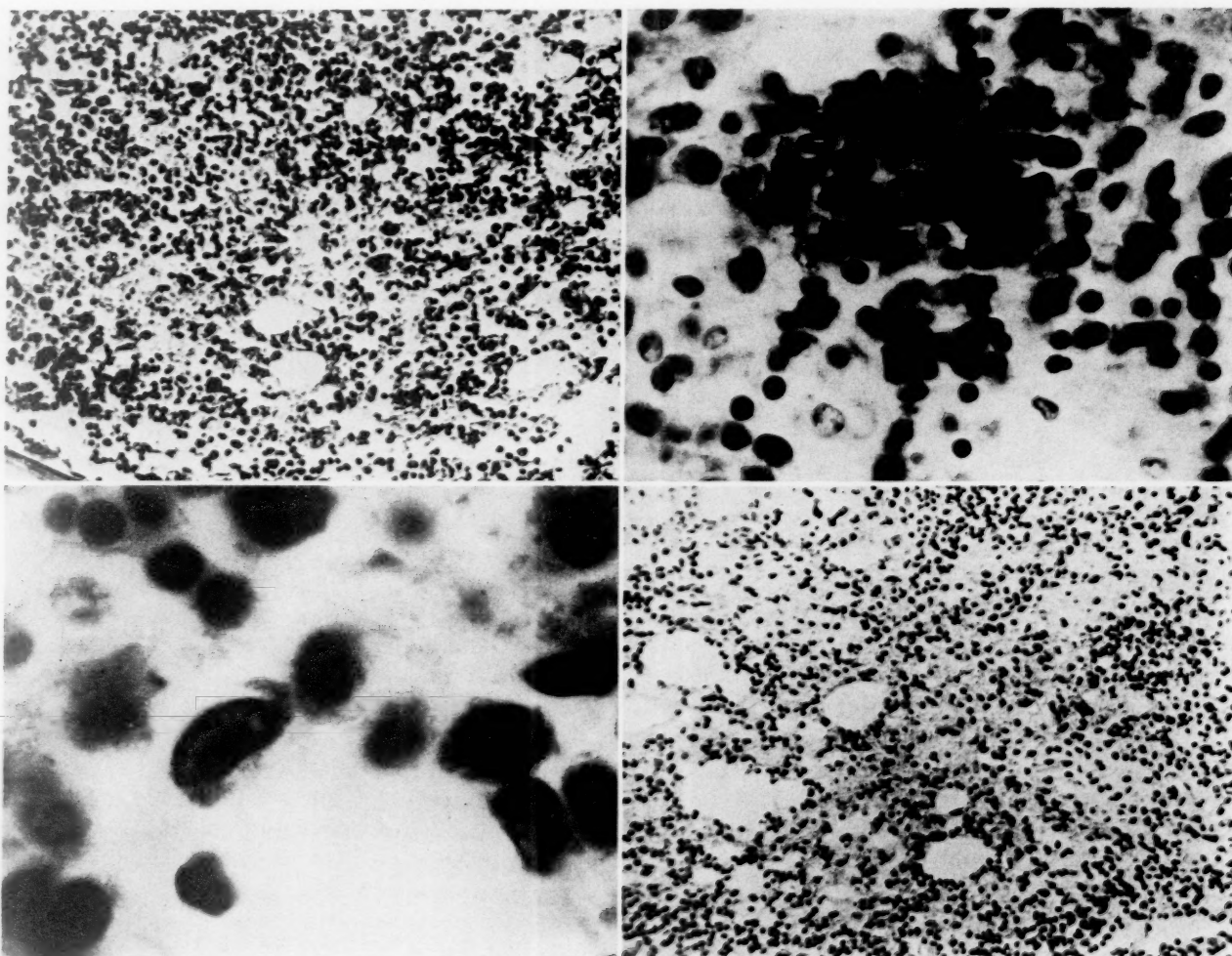


FIG. 1. Cellular marrow of the thoracic vertebra. Hematoxylin and eosin.

FIG. 2. A focal area of erythropoiesis is illustrated in the femoral marrow. Several normoblasts are present in this area. Giemsa stain.

FIG. 3. Immature cells are illustrated in the bone marrow. They had round or irregularly shaped nuclei and contained a moderate amount of basophilic cytoplasm. The identity of these cells was not established. Giemsa stain.

FIG. 4. The mesenteric lymph node is atrophic and contains numerous immature cells. A few lymphocytes are illustrated among these cells. Hematoxylin and eosin.

pleural cavity (250 cc.) and the left pleural cavity (150 cc.). Petechiae and ecchymotic areas were found on all the serous surfaces.

Both lungs contained numerous, circumscribed, small (1.5 cm.) nodules which appeared hemorrhagic on cut section. The remainder of the lung parenchyma was congested. The kidneys were pale and contained hemorrhagic areas in the pelvis. The liver weighed 2,100 gm. and had a small subcapsular hemorrhage in the right lobe. The spleen was moderately enlarged and weighed 240 gm. Malpighian bodies were not visible on the cut surface of the spleen. The gastrointestinal tract contained altered blood. Petechiae with areas of ecchymoses were

present in the mucosa of the stomach. Both ovaries contained large hemorrhagic cysts. The mesenteric lymph nodes appeared small and atrophic. The bone marrow was reddish brown in color and appeared normal on gross examination. Small focal, subarachnoid hemorrhages were found predominantly over the right temporal region.

DR. PAUL E. LACY: The degree of cellularity of the bone marrow of the ribs, sternum, thoracic vertebra and femur appeared relatively normal when it was examined with the lower powers of magnification. (Fig. 1.) The identity of the different cells within the marrow was extremely difficult to establish. A few focal areas of eryth-

ropoiesis was present in the femoral marrow. (Fig. 2.) Scattered megakaryocytes and numerous plasma cells were also present in the different section of the marrow. In addition to these elements, there were numerous immature cells which had round or irregularly shaped nuclei and contained varying amounts of moderately, basophilic cytoplasm. (Fig. 3.) We were unable to establish the identity of these cells. They could be either donor cells which were repopulating the marrow or leukemic cells which had escaped the effect of the radiation. Nowell et al.\* found that hematopoietic activity of donor cells could be demonstrated in radiated mice within five to seven days after injecting marrow obtained from rats. He was able to identify the donor cells since they were alkaline phosphatase positive while those of the mice were negative. In this particular patient, we had no distinctive label to use for identification of donor cells.

The mesenteric lymph nodes were atrophic, the germinal centers were absent and only a few lymphocytes were present in the cortex. (Fig. 4.) Numerous immature cells were present in the lymph nodes and they resembled the immature cells found in the bone marrow. Again we were unable to establish the identity of these cells. They could be either immature cells of the reticuloendothelial system which were repopulating the lymph node or they could be leukemic cells. Since monoblasts were apparently found in the peripheral blood of this patient following radiation, it would appear most probable that these immature forms were leukemic cells.

The white pulp of the spleen was markedly atrophic and only a few lymphocytes were found around the central arteries. The red pulp contained plasma cells, reticuloendothelial cells and immature cells. Phagocytized red blood cells were present in some of the reticuloendothelial cells.

The liver appeared normal except for a few focal areas which contained lipid. Immature cells were not found in the portal areas or within the liver parenchyma. The nodules observed on gross examination of the lung were composed of hemorrhagic areas with some evidence of necrosis of lung parenchyma in the centers of the lesion. Numerous fungi were present in all the lesions and extended through the walls of the blood

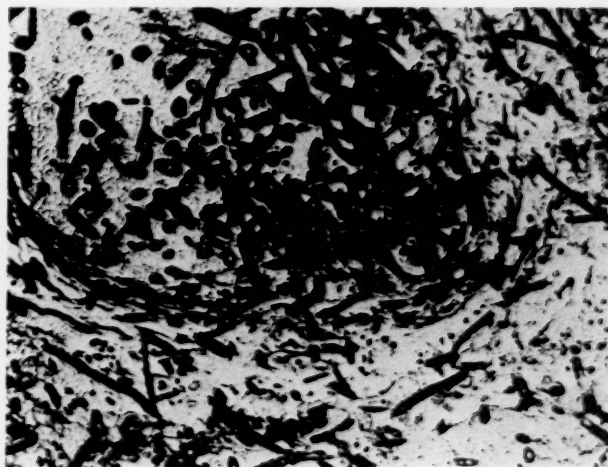


FIG. 5. Numerous fungi are illustrated in the lumen of a pulmonary artery. They are extending through its wall into the surrounding parenchyma. Periodic acid-Schiff stain.

vessels. (Fig. 5.) These organisms did not grow in the cultures obtained at autopsy so a positive identification of them could not be obtained. Morphologically they resembled *Aspergillus*.

**Final Diagnosis:** History of acute monocytic leukemia; history of total body Betatron radiation (400 r) twenty-one days before death; history of infusion of bone marrow twenty days before death; petechiae and ecchymoses of the skin of the periorbital region, abdomen, and thighs; serous surfaces, and mucosa of the stomach; pallor; altered blood in stomach and gastrointestinal tract; multiple petechiae and ecchymoses of mucosa of stomach; subcapsular ecchymoses of the kidneys and right adrenal; subcapsular hematoma, liver; ecchymosis, diaphragm and subendocardium of left ventricle; hemorrhagic cysts, ovaries; subarachnoid hemorrhage, right temporal lobe; cellular bone marrow containing (1) a few foci of erythropoiesis, (2) scattered megakaryocytes, (3) plasma cells and (4) many immature cells; atrophy of lymph nodes with many immature cells present; atrophy of malpighian bodies of spleen; subconjunctival hemorrhages; hydroperitoneum, 990 cc. slightly cloudy serous fluid; hydrothorax 600 cc. serous fluid; fatty metamorphosis of the liver, slight, 2110 gm.; pallor of kidneys with hemorrhages in the pelvis; needle puncture marks, sternal area (history of sternal puncture); needle puncture marks with ecchymosis, both antecubital fossa, forearms, wrists and left internal malleolar area; and multiple hemorrhagic areas of lungs containing fungi resembling *Aspergillus*.

\* NOWELL, P. C., COLE, L. J., ROAN, P. L. and HABERMAYER, J. G. The distribution and *in situ* growth pattern of injected rat marrow in X-irradiated mice. *J. Nat. Cancer Inst.*, 18: 127-137, 1957.

# Case Reports

## Persistent Atrial Tachycardia with Atrioventricular Block\*

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**A**TRIAL tachycardia with atrioventricular block is seen in three general clinical settings. First, it may occur paroxysmally in patients in whom no underlying heart disease is demonstrable. In this setting, conduction of each atrial impulse to the ventricle is the more usual finding. Secondly, it is seen as a manifestation of digitalis toxicity. Thirdly, in some patients with organic heart disease this arrhythmia is due to the underlying heart disease.

In the case to be reported herein, a number of features of the course and management should be particularly noted. First, the atrial tachycardia with atrioventricular block persisted for an unusually long period. Secondly, this case demonstrates the problem of assessing the role of digitalis in the genesis of this arrhythmia. In this case, a clear-cut resolution was possible and the efficacy of administration of digitalis in treatment of atrial tachycardia with atrioventricular block when the rhythm is not a manifestation of digitalis toxicity is well demonstrated.

### CASE REPORT

N. M. (B.H. 51151-56), a sixty-seven year old white man, was admitted to the Second (Cornell) Medical Division, Bellevue Hospital, for the first time on October 1, 1956, because of swelling of the legs, abdomen and scrotum of four weeks' duration. Five years previously he had passed a physical examination for life insurance. He was a moderately heavy drinker, admitting to 3 pints of wine per week, but maintained that his diet had been adequate until the past few weeks. In the three months before admission, his weight had increased from 230 to 254 pounds. He denied any past history of cardiac symptoms or disease.

On examination the patient was an obese man with

anasarca, and was in moderate respiratory distress. The temperature was 99.0°F., pulse 108 per minute and regular, respirations 34 per minute, and blood pressure 120/80 mm. Hg. Pertinent physical findings included: arteriolar narrowing and arteriovenous nicking of the retinal vessels, distended neck veins, dullness to flatness with decreased breath sounds and fine and medium inspiratory and expiratory rales bilaterally at the lung bases. The point of maximal cardiac impulse and the left border of cardiac dullness were 12 cm. to the left of the mid-sternal line in the fifth intercostal space. The heart sounds were of fair intensity with the second sound louder in the pulmonic than in the aortic area. At the apex the first sound was of lower intensity than the second. A medium pitched systolic murmur of moderate intensity was heard at the apex with radiation toward the base. No other murmurs were heard. There was no rub. The abdomen was protuberant, and a fluid wave and shifting dullness were present. The liver edge was percussed 3 cm. below the right costal margin. There was edema of the scrotum and 4-plus pitting edema of the legs.

Urinalysis showed a specific gravity of 1.021, 3-plus proteinuria, negative Benedict test for reducing substances, a few red blood cells and many white blood cells per high power field. The hemoglobin was 12.2 gm. per cent, red blood cells, 3.6 million per cu. mm., hematocrit 40 per cent, white blood cells, 5,000 per cu. mm. with 58 per cent mature polymorphonuclears 4 per cent band forms, 30 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils on differential count. Venous pressure on admission was 255 mm. of saline and the circulation time, arm to tongue (decholin®), was thirty-five seconds.

The blood urea nitrogen ranged from 20 to 26 mg. per cent during the hospital stay. Electrolyte determinations on admission were: sodium 140 mEq./L., potassium 3.8 mEq./L., chloride 109 mEq./L. and CO<sub>2</sub> combining power 23.5 mEq./L. Serial determinations throughout the course were within normal

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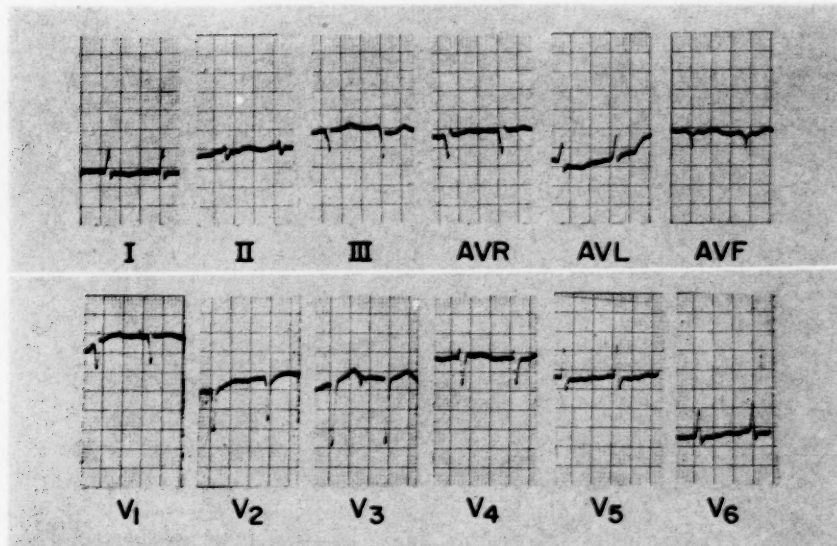


FIG. 1. Electrocardiogram taken on admission. Atrial activity is poorly defined. The Q in III and AVF is evidence of previous myocardial infarction.

limits. Detailed study of plasma and urinary potassium levels are presented in Table I. The blood Mazzini test for syphilis was negative. Other determinations included: initial total protein of 4.9 gm. per cent with an albumin of 2.7 gm. per cent and globulin of 2.2 gm. per cent subsequently rising to 6.4 gm. per cent with

TABLE I  
FIRST ADMISSION \*

Date	Body Weight (lb.)	24-Hour Urine Volume (cc.)	Urinary K <sup>+</sup> Excretion (mEq./24 hr.)	Supplementary Oral KCL (mEq.)	Plasma K <sup>+</sup> (mEq./L.)
10/1/56	254	.....	.....	90	3.6
10/2/56	246	2800	17.5	55	3.4
10/3/56	241	2100	42.2	55	3.9
10/4/56	235	2100	48.4	40	3.8
10/5/56	227	3500	61.2	67	4.25
10/6/56	215	3200	.....	55	.....
10/7/56	211	3400	.....	55	.....
10/8/56	204	3500	.....	55	4.4
10/9/56	197	3800	.....	55	.....
10/10/56	190	2700	73.0	55	.....
10/11/56	186	1500	.....	..	4.3
10/15/56	180	800	.....	..	4.0
10/22/56	182	.....	.....	..	4.4
10/24/56	178	.....	.....	..	4.0

\* During diuresis with weight loss of 76 pounds, dietary potassium was supplemented by oral KCL. Note that plasma potassium concentration remains within normal limits.

an albumin of 3.1 gm. per cent and globulin of 3.3 gm. per cent. Alkaline phosphatase was 3.3 units, cephalin flocculation initially 4-plus, subsequently 1-plus, icterus index 6 units, cholesterol 140 mg. per cent with 57 per cent esterification. Prior to discharge the bromsulphalein retention was 10 per cent in forty-five minutes.

X-ray of the chest taken on admission showed en-

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## AVF



FIG. 2. Strip from electrocardiogram taken on October 17, 1956. Arrows point to small P waves that were not appreciated at the time of original interpretation.

largement of the transverse diameter of the heart, congestive changes in both lung fields and a left pleural effusion.

The plasma volume (T1824) was markedly increased.

An electrocardiogram taken on admission revealed a rhythm thought to represent a regular supraventricular tachycardia with poorly defined atrial activity, probably sinus tachycardia with first degree heart block. The presence of a Q<sub>III</sub>, Q<sub>AVF</sub> was interpreted as evidence of previous myocardial infarction. (Fig. 1.) Vectorcardiography confirmed this impression.

The patient was placed on a regimen including complete bed rest and a low salt diet. He was given 1.4 mg. of digitoxin during the first twenty-four hours, and a mercurial diuretic. Subsequently he was maintained on digitoxin, 0.1 and 0.2 mg. on alternate days, and received further injections of a mercurial diuretic. This regimen resulted in clinical improvement associated with weight loss from 254 to 179 pounds.

On October 17, 1956, the electrocardiogram re-

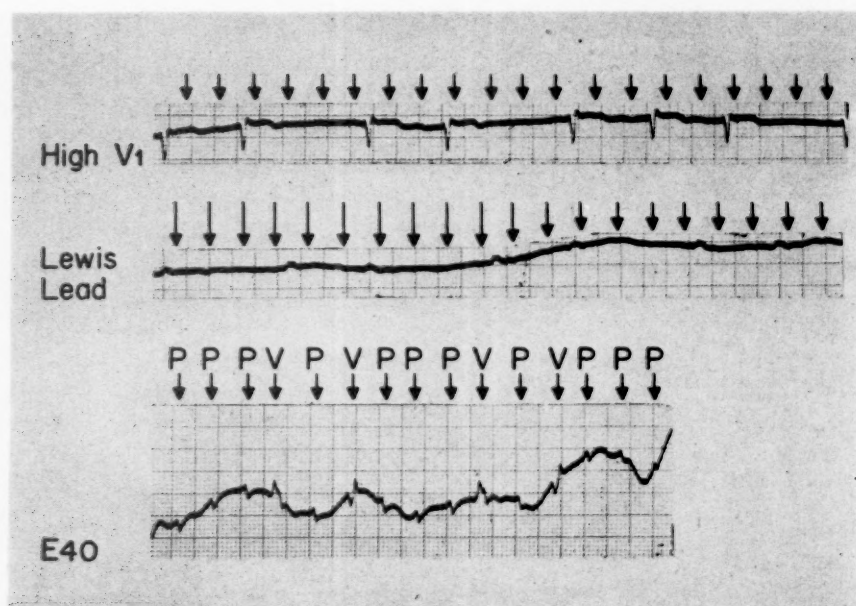


FIG. 3. After the second admission, exploratory chest leads and a Lewis lead suggested regular atrial activity. Esophageal lead 40 cm. from the anterior nares confirmed the presence of a regular atrial tachycardia. Atrial contractions are indicated by P and ventricular complexes by V.

vealed an irregular rhythm interpreted as a sinus tachycardia with first degree heart block, frequent atrial premature contractions and occasional ventricular premature contractions. However, atrial activity was poorly defined. (Fig. 2.) On October 22, 1956 the electrocardiogram again revealed an irregular rhythm, interpreted as atrial fibrillation with a moderate ventricular rate. Esophageal leads to define the arrhythmia further were not obtained during this admission.

On October 27, 1956, the patient was discharged to clinical follow-up on a regimen including digitoxin 0.1 and 0.2 mg. on alternate days. Following discharge he failed to adhere to a salt restricted diet and did not return to the clinic.

Three months later, January 21, 1957, he was readmitted to the hospital, again in congestive heart failure. Two weeks earlier a non-productive cough had developed, and one week prior to admission edema of the legs had developed which progressed to involve the scrotum and abdomen. He had noted increasing dyspnea on exertion. Digitoxin had been taken as prescribed until two days prior to readmission when his supply ran out. There had been no nausea, vomiting or visual disturbances.

His appearance was similar to that on the first admission, and the findings on physical examination were essentially unchanged, including the presence of anasarca.

Laboratory data obtained on admission included 2-plus proteinuria, a venous pressure of 235 mm. of saline and circulation time, arm to tongue (decholin), twenty-eight seconds.

The electrocardiogram taken on admission was interpreted as showing an irregular supraventricular rhythm, probably atrial fibrillation with frequent ventricular premature contractions, giving rise to a bigeminal rhythm. The form of the record was otherwise unchanged from the previous admission.

TABLE II  
SECOND ADMISSION\*

Date	Weight (lb.)	24-Hour Urine Volume (cc.)	Supplementary Oral KCL (mEq.)	Plasma K <sup>+</sup> (mEq./L.)
1/21/57	226	800	60	...
1/22/57	225	800	40	...
1/23/57	225	4500	40	4.6
1/24/57	220	4350	60	4.5
1/25/57	208	4650	..	5.0
1/26/57	201	4000	..	...
1/27/57	193	3300	60	...
1/28/57	191	4000	30	4.4
1/29/57	185	4000	..	...
1/30/57	179	2800	..	...
1/31/57	179	3100	..	...
2/1/57	177	....	..	4.1
2/2/57	173	....	..	...
2/8/57	173	....	..	4.3

\* During diuresis with weight loss of 53 pounds, supplements of KCL were given orally. Plasma potassium concentration remained within normal limits.

In view of the patient's increasing cardiac decompensation and the presence of frequent ventricular premature contractions with bigeminy occurring in a setting of daily digitalis therapy, it was considered that digitoxin intoxication was present. Accordingly, digitoxin was withheld and his congestive heart failure was managed with bedrest, salt free diet and mercurial injections. A good clinical response was achieved. Because of the evidence of ventricular irritability on electrocardiogram, potassium chloride was given orally during the brisk diuresis to prevent potassium depletion with its possible enhancement of manifestations of digitoxin intoxication. (Table II.)

Exploratory chest leads taken on the third hospital day revealed a regular alteration in R-R intervals and small waves suggesting regular atrial activity. At this time an esophageal lead was passed and the tracing obtained clearly revealed an atrial tachycardia with an atrial rate of 215 per minute, varying 2:1 and 3:1 atrioventricular block, and frequent ventricular premature contractions. (Fig. 3.) The ventricular rate was 85 per minute. Carotid sinus pressure did not alter the atrial rate but increased the atrioventricular block to 3:1 and 4:1.

Review of previous tracings at this time suggested that the atrial tachycardia had probably been present since October 17, 1956, the time of initial hospitalization and digitalization. (Fig. 2.)

In view of the good response to other therapy and the possibility of digitalis intoxication as a basis for the arrhythmia, digitoxin was further withheld for thirty days. Esophageal electrocardiograms continued to show an atrial tachycardia with atrial rate ranging from 180 to 230 per minute. At the end of this period, the atrial tachycardia was still present and frequent premature ventricular contractions were still recorded. The atrial rate was 208 per minute, but the atrioventricular conduction was now predominantly 2:1, and the ventricular rate had increased to 107 per minute. (Fig. 4.) Previously, while receiving digitalis the atrioventricular conduction had been 3:1 and 4:1 and the ventricular rate 85 per minute.

It was evident that the underlying heart disease and not digitalis was responsible for the atrial tachycardia. In view of the undesirable increased ventricular rate, it was believed that digitalis administration was indicated in order to increase the atrioventricular block and slow the ventricular rate. Accordingly the patient was redigitalized with digitoxin during the next three days. Subsequent electrocardiograms have revealed atrial tachycardia with predominantly 3:1 atrioventricular conduction and a ventricular rate of 74 per minute. (Fig. 5.)

When last seen in follow-up (March 12, 1957), the atrial tachycardia with atrioventricular block was still present—a duration of six months. The patient was taking a maintenance dose of digitoxin daily and was free of signs and symptoms of congestive failure.

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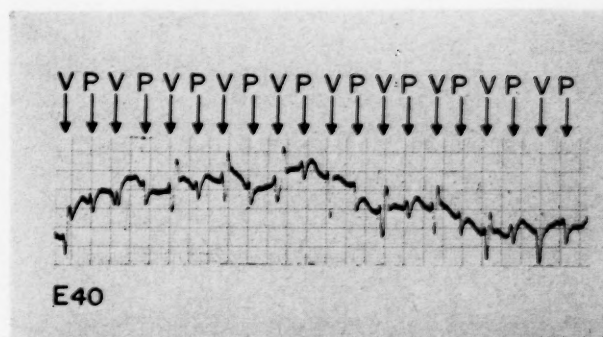


FIG. 4. Esophageal lead shows persistence of the atrial tachycardia with predominantly 2:1 atrioventricular conduction and an increased ventricular rate. All the P waves are not indicated by arrows. At the time of this record digitoxin had not been administered for thirty days. (P = atrial contraction, V = ventricular contraction.)

#### COMMENTS

In that group of patients with atrial tachycardia and no demonstrable underlying heart disease, there is usually a 1:1 relationship between atrial and ventricular activity [8,11-13]. Although characteristically recurrent, individual episodes of this arrhythmia last for hours to a few days in most instances. In rare instances, the atrial tachycardia in these patients without demonstrable underlying heart disease may persist for prolonged periods. Schwartz and Levine [2] have described a patient in whom atrial tachycardia has persisted for twenty-five years. In this type of patient, atrioventricular block generally develops either spontaneously or, more commonly, as a result of digitalis administration given in an attempt to revert the tachycardia [3-9]. The age of the patient in the case reported herein and the prior occurrence of myocardial infarction make it evident that he does not fall into this group of patients.

Atrial tachycardia as a manifestation of digitalis toxicity is usually associated with atrioventricular block. Since the first report in 1932, many cases of the induction of this arrhythmia by digitalis have been published [8,15,16,18]. The studies by Lown and Levine in 1953 have emphasized this relationship, as well as the importance of potassium balance as a significant factor in the effect of digitalis on the heart rhythm [19,20]. In their experience, and that of others [6,16,18], atrial tachycardia with atrioventricular block produced by digitalis almost invariably is reverted by potassium administration. Bettinger *et al.* [16] have recently reported

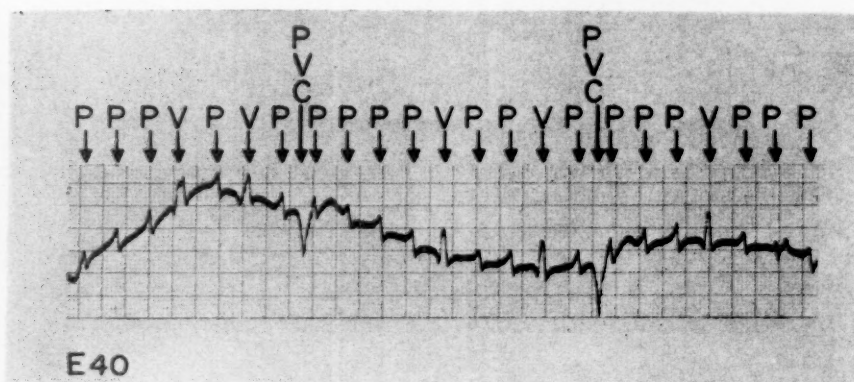


FIG. 5. Following redigitalization with digitoxin, the atrial tachycardia persisted, with an increase in the atrioventricular block and consequent slowing of the ventricular rate. (P = atrial activity, V = ventricular activity, PVC = premature ventricular contraction.)

that potassium is effective in abolishing some arrhythmias whether or not digitalis administration is associated with their occurrences. Seven patients in their study had atrial tachycardia with atrioventricular block of more than twenty-four hours' duration, and two of the three who had not received digitalis reverted to normal sinus rhythm during potassium chloride administration. Four patients reported were receiving digitalis when the arrhythmia was treated. Three reverted to their previous rhythm. The fourth did not revert, but the atrial rate slowed after 29 mEq. of potassium chloride had been administered. Atrial slowing was the first change noted by Lown and Levine in the reversion of atrial tachycardia, and perhaps further potassium administration would have achieved reversion in this particular case.

These results suggest that potassium administration has limited value as a diagnostic aid in determining the role of digitalis in causing atrial tachycardia with atrioventricular block in a given clinical situation. It appears that potassium administration may be effective regardless of the underlying etiology. However, when digitalis toxicity is the basis, particularly in the setting of a negative potassium balance, potassium administration invariably slows the atrial rate and usually re-establishes the pre-existing rhythm. In the case reported here, potassium salts were administered during diuresis to maintain potassium balance. (Fig. 1.)

The patient reported herein falls into that group of patients with organic heart disease in whom atrial tachycardia with atrioventricular block exists as the basic rhythm, unrelated to digitalis administration. In thirty-nine of fifty-

one patients reported by Lown and Levine [20], digitalis overdose or negative potassium balance in digitalized patients was the factor responsible for this arrhythmia. In six of the remaining twelve, atrial tachycardia with atrioventricular block persisted for more than one month. Since these fifty-one patients represented the experience of a large clinic over an eleven-year period, it is evident that atrial tachycardia with atrioventricular block is uncommon as a basic rhythm in patients with organic heart disease. In this group, many of whom are receiving digitalis when this arrhythmia is first recognized, it is important to assess the role of digitalis in the development of the tachycardia. If digitalis effect is responsible, further administration may produce a fatal arrhythmia [6,12]. However, if digitalis is not involved in the production of the atrial tachycardia, withholding it may result in a decrease in the atrioventricular block and an undesirable increase in the ventricular rate. In some cases, increased doses of digitalis are necessary to produce a sufficient degree of atrioventricular block to achieve the desired ventricular rate. The case reported herein clearly demonstrates these principles. When digitalis was withheld and its effect dissipated, the ventricular rate increased (Fig. 4) and the patient was clinically more symptomatic. Redigitalization resulted in the re-establishment of 3:1 and 4:1 atrioventricular conduction (Fig. 5) and the patient's clinical state improved.

The setting in which the atrial tachycardia occurs provides the most important clue as to the role of digitalis in its production. Where the patient has been on unusually large amounts of digitalis, digitalis withdrawal is warranted.

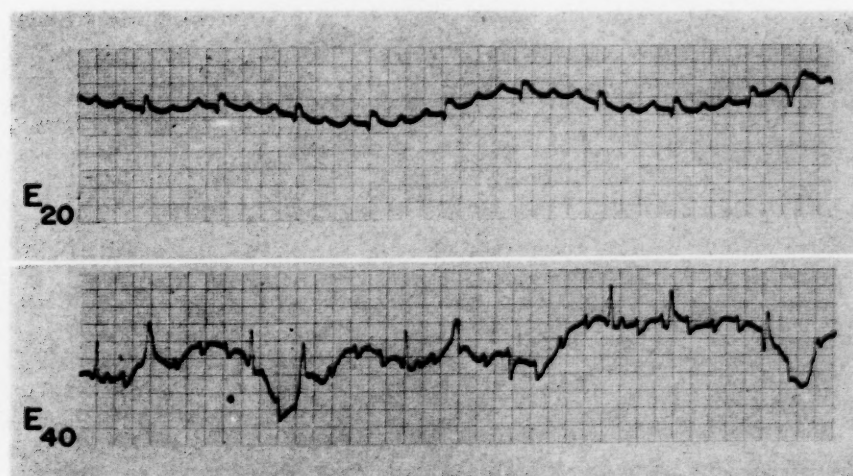


FIG. 6. Esophageal leads taken at two levels simultaneously demonstrate a "sine-wave" type baseline undulation at  $E_{20}$  and an isoelectric period between P waves at  $E_{40}$ . See comments.

This is especially true in the presence of any other evidence of digitalis intoxication.

Potassium administration may be added to the therapeutic program, particularly in the presence of a low serum potassium concentration, or in a setting likely to have produced a negative potassium balance. In the light of reports cited above, however, it is evident that "a trial of potassium" must be regarded as inconclusive. Indeed it may be dangerous. Success with potassium does not mean that digitalis is responsible, and such an interpretation could lead to undesirable consequences.

The case reported posed just such a problem. The arrhythmia was first recognized in the course of a marked diuresis. The patient had been taking digitoxin, and frequent premature ventricular contractions were present. Potassium administration reduced the ventricular irritability, but the atrial arrhythmia persisted unchanged. Had the arrhythmia been defined on the patient's previous admission, its chronicity would have lent support to the impression that it was independent of digitalis effect. In Lown and Levine's series [20], only one case of the thirty-nine in which the atrial tachycardia was due to digitalis effect persisted for as long as one month. In that particular case, it is not reported whether or not potassium was administered.

Much has been written on the subject of the distinction between atrial tachycardia and atrial flutter. By electrocardiographic criteria [2,9] the rhythm in the patient reported on is atrial tachycardia with atrioventricular block. How-

ever, its chronicity and its response to carotid sinus stimulation and to digitalis are more in keeping with the clinical behavior of flutter. This discrepancy supports the contention that a qualitative distinction between atrial tachycardia and atrial flutter may be unwarranted.

In this patient the atrial rate varied from 180 to 240 per minute, which in itself changes the electrocardiographic diagnosis from atrial tachycardia to flutter by some criteria. In atrial tachycardia the P-P interval is usually stated to be isoelectric, while atrial flutter is said to be characterized by a continually undulating baseline producing a sine-wave type of atrial activity. Prinzmetal et al. [12] have shown this configuration to be the result of rapid alteration of  $p'$  and Tp complexes. Keshan et al. [22] have also shown that the electrocardiographic representation of atrial repolarization is a function of atrial rate. They find that at more rapid atrial rates the Tp complex immediately follows the P wave and is of opposite polarity producing the sine-wave undulations usually associated with atrial flutter. Thus it appears that the nature of the recording of atrial activity is not related to the basic mechanism of the arrhythmia which is present, but rather is an expression of the rate of atrial activity. In this regard it is noteworthy that, in one record in the reported patient, esophageal leads at different levels revealed both the isoelectric P-P interval considered characteristic of atrial tachycardia and the sine-wave type of atrial activity considered characteristic of atrial flutter. (Fig. 6.)

Prinzmetal [11,12] conceives of all of the atrial

arrhythmias as arising from an ectopic focus located in the atrial myocardium, discharging repetitively at varying rates and with varying atrioventricular relationships. The resultant rhythm would then be the expression of the relative contributions of the multiple factors which influence the duration of the refractory period, rhythmicity, and conduction velocity of the sino-auricular and atrioventricular nodes and the atrial musculature. These factors include the interplay of vagal and opposing forces, digitalis effect, and the effects of disease on these structures. By the terminology resulting from this unified concept [12] the rhythm in the patient presented would be described as "atrial tachycardia from a caudal atrial focus at a rate of 180 to 240 per minute with varying atrioventricular block." This terminology avoids the necessity of making the arbitrary choice between atrial tachycardia and flutter.

## SUMMARY

1. A case history is presented of a patient in whom atrial tachycardia with atrioventricular block has persisted for a period of six months.

2. The case serves to emphasize the importance of determining the role of digitalis in the etiology of this arrhythmia, and illustrates the beneficial therapeutic effect of digitalis administration when the arrhythmia is not digitalis-induced.

3. Mechanisms of production of atrial tachycardia and atrial flutter are discussed, and data from the case report are cited to support the unitarian concept of their production.

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# Intestinal Malabsorption Following Temporary Occlusion of the Superior Mesenteric Artery\*

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CONSIDERABLE interest has recently been displayed in the physiology and diseases of the small bowel. It has been established that the clinical picture variously termed sprue, idiopathic steatorrhea, chronic jejunoileal insufficiency, and the malabsorption syndrome may result from many different pathological lesions. These include chronic pancreatitis, pancreatic cancer, lymphoma and other reticuloses, tuberculosis, Whipple's disease, intestinal diverticulosis and fistulae, and the results of major abdominal surgery, especially gastrectomy. In none of these instances, however, is there adequate knowledge of the pathologic physiology resulting in malabsorption.

The present paper reports a further sequence of events leading to malabsorption, and one of considerable interest in throwing light upon the physiologic mechanisms involved. In two patients, temporary occlusion of the superior mesenteric artery occurred and was surgically relieved. In each case the patient later was shown to have intestinal malabsorption. The clinical and metabolic data in these cases form the substance of this report. The surgical techniques will be described elsewhere [1,2].

## CASE REPORTS

CASE 1. (MGH No. 94-70-20). A fifty-two year old white married woman was admitted to the Massachusetts General Hospital on October 19, 1956, suffering from epigastric pain, vomiting, and blood-stained bowel movements for the previous thirty-two hours. She had been known to have rheumatic heart disease with mitral stenosis and auricular fibrillation for five years, but at no time had there been evidence of cardiac failure.

Five days prior to admission there had developed sudden left hemiplegia without loss of consciousness.

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The day before admission she noted sudden onset of epigastric pain with persistent vomiting of non-bloody material. Six hours after the onset of this pain she passed fresh blood per rectum. The next day she had further bloody diarrhea and was referred to the hospital that evening. Direct questioning of both the patient and her family on this and subsequent occasions elicited no history of previous alimentary disorder.

On admission, the patient appeared acutely ill. The temperature was 101°F., peripheral pulse 110/minute with atrial fibrillation, and blood pressure 150/90 mm. Hg. She had a left hemiparesis involving face, arm and leg. Her heart was enlarged, and she had mitral stenosis and incompetence. There were no signs of cardiac failure. Her abdomen was diffusely tender, but no abnormal mass or viscus was palpable. No free fluid could be detected in the peritoneal cavity. Peristaltic sounds were decreased but not completely absent. Digital examination showed the rectum to contain dark red blood. The hemoglobin was 13.2 gm. per cent; white cell count, 16,800 per cu. mm. with a polymorphonuclear leukocytosis; serum amylase, 2 Russell units; serum bilirubin, 0.7 mg. per cent.

The diagnoses of rheumatic heart disease with mitral stenosis and incompetence, atrial fibrillation, cerebral embolus, mesenteric embolus and infarction were made.

Laparotomy was performed two hours after admission (thirty-four hours after the patient first noted abdominal pain). On opening the abdomen the small bowel appeared blue-gray in color and no vascular pulsation was detectable in it. An embolus was found in the superior mesenteric artery distal to the origin of the mid-colic artery. The artery was opened, the clot removed, and heparin was injected distally into the vessel. Following this, pulsations were felt distal to the site of embolectomy, but not extending to the arcuate arteries. The bowel color improved, and it was decided not to undertake massive resection of the jejunum and ileum. A second laparotomy was planned and undertaken the next day (October 21),

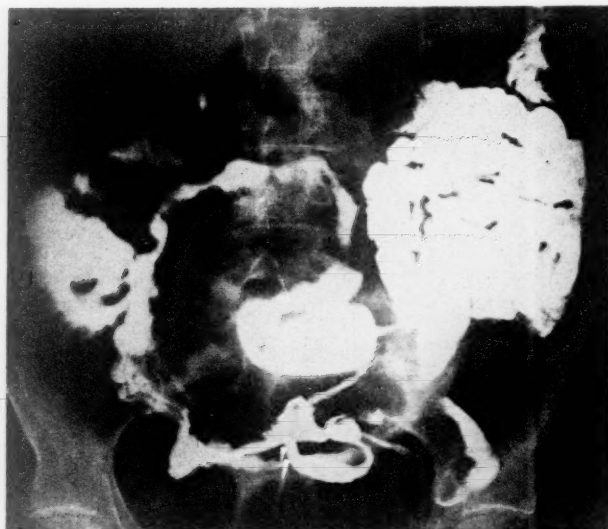


FIG. 1. Case 1. X-ray film of small bowel taken on November 29, 1956, showing abnormal ribbon-like pattern with pooling of barium.



FIG. 2. Case 1. Repeat film taken on December 18, 1956, showing similar changes with diffuse narrowing and loss of mucosal pattern.

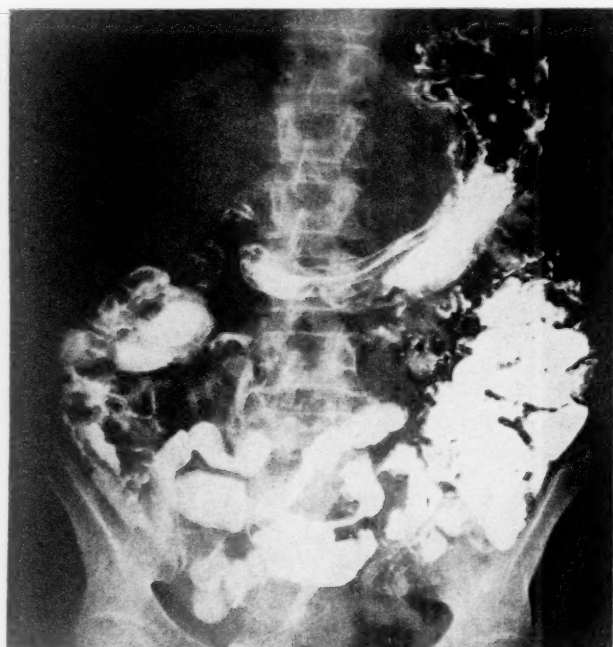


FIG. 3. Case 1. Roentgenogram taken on January 22, 1957. The gastric rugae are unusually prominent. The small bowel changes are little altered in appearance.

as there was doubt as to the viability of the gut. However, gross appearances were much improved and no resection was needed. The patient withstood both these procedures well.

She was given heparin after the operation, and later maintained on oral dicoumarol, the dosage varying from 50 to 75 mg. per day. This kept her prothrombin activity below 25 per cent of normal. She also received parenteral antibiotics in high dosage, initially penicillin 1,200,000 units and streptomycin 1.0 gm. per day, later erythromycin 400 mg. and

chloromycetin 2.0 gm. per day for twenty-six days. She received no oral antibiotics at any stage.

After the first postoperative days, her general condition improved steadily. There was little change in her neurologic status. On digitalis she maintained a slow auricular fibrillation, but no evidence of further emboli or cardiac failure was detected.

On the third postoperative day she passed a dark green semisolid stool, and further loose stools next day, after which her stools reverted apparently to normal. Stool cultures on the ninth, twelfth and thirty-sixth days grew no enteric pathogens. However, on the fifteenth postoperative day diarrhea recurred and persisted, although without causing alarm until about December 1, 1956, when the patient was found to have cheilosis, glossitis and dependent edema. Further investigation was therefore undertaken. Microscopy of the foul stool revealed a considerable increase in both split and neutral fats. X-ray examination made on November 29, 1956, showed no abnormality in the esophagus, stomach or duodenum. The small bowel was grossly abnormal; ribbon-like and irregular in pattern with pooling of barium in some loops. Barium was seen in the cecum about six hours after administration. (Fig. 1.) The patient was therefore referred for detailed metabolic studies, which were carried out from December 4, 1956, until the patient's discharge from the hospital on January 24, 1957, and again during a second admission from February 5, 1957 to February 19, 1957.

Her clinical condition during the first study period was one of slow but steady improvement, although her stools remained bulky and she continued to have some incontinence of feces. She had a good appetite and consumed 2,000 calories per day without difficulty. Further radiological examinations were made on December 18, 1956 and January 22, 1957. The find-

TABLE I  
RESULTS OF ORAL FAT TOLERANCE TESTS\*

Case No. and Date	Optical Density (units)							Vitamin A Tolerance Tests (units/ml.)						
	Fasting	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	Fasting	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.
	(65)	(73)	(83)	(129)	(134)	(241)	(193)	(0.85)	(0.99)	(1.22)	(1.24)	(1.62)	(2.68)	(3.87)
I, 12/20/56	40	.....	.....	53	69	120	142	0.51	.....	.....	0.64	1.04	1.30	1.40
3/ 8/57	40	.....	.....	118	70	125	78	0.09	.....	.....	2.43	2.44	3.40	2.04
II, 3/29/57	70	.....	.....	72	78	82	98	0.56	.....	.....	0.49	0.68	0.67	0.85

\* NOTE: Numbers in parentheses represent normal values.

ings were essentially similar to those of the initial examination (Figs. 2 and 3), except for a decrease in the transit time, barium reaching the cecum in about thirty minutes. An abdominal aortogram on January 9, 1957, showed a widely patent superior mesenteric artery, but the film was technically inadequate to demonstrate patency or obstruction of the distal arterial arcades.

During the second admission (March 5 to 19, 1957) there was little clinical or radiological change in the patient's condition except for the development of hypoproteinemia and dependent edema. These responded to intravenous administration of albumin.

When last seen in the follow-up clinic on May 13, 1958, she had no abdominal discomfort of any type, and was having one or two formed stools daily. Mitral valvotomy had been successfully accomplished in April 1958, and she had resumed housework.

**Metabolic Studies.** For convenience of presentation the metabolic data have been grouped under the following five headings: hematologic, carbohydrate metabolism, fat metabolism, protein metabolism, and miscellaneous other data. Unless otherwise specified, the technical methods employed were those in routine use at the hospital [3].

**Hematologic data:** After the initial blood loss anemia had been corrected by three transfusions, a slightly macrocytic anemia (hemoglobin, 10.5 gm. per cent; mean corpuscular volume, 107 cu. microns) developed. Plasma pepsinogen was persistently elevated (785 to 1,080 units per ml.) and tubeless gastric analysis [5] revealed the secretion of free hydrochloric acid. Initially the absorption of vitamin B<sub>12</sub> was defective (less than 1 per cent by the Schilling [6] procedure), but by March 1957 this had become normal. A month later she had normal blood counts. The serum iron was repeatedly normal.

**Carbohydrate metabolism:** An oral glucose tolerance test on December 20, 1956 was normal. The fasting blood sugar was 71 mg. per cent and the maximal rise, at one hour, was 130 mg. per cent. Impaired carbohydrate absorption was demonstrated by the d-xylose

absorption test [7]; only 3.4 and 3.2 gm. (normal  $6.5 \pm 1.2$  gm.) were excreted per five hours in December 1956 and March 1957.

**Fat metabolism:** Serum cholesterol and cholesterol ester levels were repeatedly normal, but the serum carotene was persistently reduced.

The results of oral fat tolerance tests\* are shown in Table I. Repeated stool microscopy showed increased amounts of fats and soaps, varying from slight to gross. Fat balance studies were made on seven occasions, fecal fat being measured by the method of van der Kamer [9]. The results are shown in Table II.

These various studies show clearly that this patient had faulty absorption of fats and a moderate steatorrhea. Dietary fat was poorly absorbed and fecal fat increased, while most of the blood lipid components examined were decreased. Lipid absorption improved during the period of observation.

**Protein metabolism:** Hypoalbuminemia, with dependent edema developed in the patient during the study periods. This responded to intravenous albumin administration. Paper electrophoresis showed the serum protein pattern to be normal.

Adequate nitrogen balances were obtained on two occasions, other attempts being unsatisfactory due to contamination of the feces with urine. In these experiments the fecal nitrogen was at or above the upper normal limit of 2 gm./day, being 1.9 gm./day (period II), and 3.0 gm./day (period V) on daily protein intakes of 72 and 89 gm. respectively.

**Other data:** Plasma electrolyte values were normal except for mild respiratory alkalosis following the

\* A fasting subject is fed 30 cc. of olive oil to which is added 3.5 cc. of vitamin A concentrate (227,500 units). Blood samples are taken fasting and then hourly for six hours. Luncheon is served four hours after the test meal. Serum turbidity is then read in a Coleman photoelectric colorimeter with a 620 filter against a water blank. Optical density  $\times 1,000$  = units of turbidity. The normal turbidity curve is the mean of such tests in ten normal subjects and the vitamin A curve of twenty normal subjects [8].

patient's postoperative respiratory infection. The serum calcium was repeatedly about 8.0 mg. per cent. Her serum phosphorus was initially low at 2.0 mg. per cent, later rising to 4.1 mg. per cent. The alkaline phosphatase fell to normal.

TABLE II  
FAT BALANCE STUDIES

Period No.	Inclusive Dates	Mean Daily Fat Intake (gm.)	Fecal Fat	
			(gm./day)	(per cent of intake)
Case I				
I	Dec. 21-27, 1956	87.5	21.4	24.5
II	Dec. 29-Jan. 4, 1957	92.6	10.7	11.5
III	Jan. 9-12, 1957	103	12.1	11.7
IV	Jan. 14-20, 1957	84.2	8.5	10.1
V	Mar. 10-13, 1957	135	14.9	11.1
VI	Mar. 14-17, 1947	142	21.2	15.0
VII	Feb. 11-14, 1958	112	4.9	4.4
Case II				
I	Apr. 1-4, 1957	81.2	19.3	23.8
II	Apr. 5-9, 1957	92.5	15.6	16.8
III	Apr. 9-13, 1957	92.5	15.1	16.3
IV*	Apr. 13-15, 1957	100	13.7	13.7
V*	Apr. 15-19, 1957	107.5	25.7	23.9
VI	Apr. 8-11, 1958	100	5.7	5.7

\* Oral pancreatic extract.

Liver function tests (except for serum protein levels) were normal. Bromsulphalein retention was 2 per cent. The blood non-protein nitrogen was within normal limits during the periods of study. The blood creatinine was 0.8 mg. per cent. Urinalysis showed transient proteinuria at the height of her illness, at which time she had acute pyelonephritis.

*Comment:* The sequence of events in this case is strong presumptive evidence that the malabsorption syndrome in this patient was due to a temporary episode of obstruction of the superior mesenteric artery. This obstruction lasted thirty-four hours from the onset of her pain to successful mesenteric embolectomy. Re-establishment of circulation into the superior mesenteric artery was shown directly at the second laparotomy and later by aortography. Gross intestinal malabsorption was noted two weeks after the ischemic episode. Moreover, the radiologic changes observed in the small bowel on three occasions, postoperatively closely resembled those known in other cases to result from infarction of the small bowel [10]. In the present case, however, they were diffuse rather than segmental and correspond well with the distribution of the superior mesenteric artery.

The absorption defect produced was multiple, involving fat, carbohydrates and protein as well as vitamin B<sub>12</sub>, although the different nutrients were affected in varying degree. It is noteworthy that there was little if any effect on serum electrolyte levels; this has also been seen after massive resection of the small bowel [17].

**CASE II.** (MGH No. 95-69-36). A fifty-four year old white man underwent end-to-side aortic, iliac and left superficial femoral homografting for bilateral thrombosis of the external iliac arteries (Leriche syndrome) on January 30, 1957. His blood pressure and electrocardiogram were normal preoperatively. He had had no alimentary symptoms following suture of a perforated duodenal ulcer in 1951.

At the time of the arterial surgery it was noted that good pulsations were present in the abdominal aorta, common iliac and hypogastric arteries, but that the inferior mesenteric artery was thrombosed. The spleen, kidneys, liver, stomach and small and large bowel were grossly normal. The left femoral graft thrombosed and required regrafting the next day. The patient withstood these procedures well.

Following this second operation the patient's condition was good at first. Peripheral pulses were palpable, and oscillometry showed good pulses in both legs. However, on the fourth postoperative day his temperature rose to 101°F. He complained of severe cramping abdominal pain, and passed a liquid stool containing blood and mucus. Bowel sounds were present, and he had no clinical signs of peritonitis. He received at this time large dosages of antibiotics, including penicillin, streptomycin, chloromycetin® and erythromycin. His fever and abdominal pain persisted, and his white blood count rose to 20,100 per cu. mm. on February 6, 1957. The serum electrolyte levels were normal. The findings in x-ray films of the abdomen were consistent with mild paralytic ileus. Stool cultures grew no pathogenic organisms. Blood cultures were negative. Antibiotic therapy was discontinued, but the patient continued to have frequent loose stools.

On the sixteenth postoperative day (February 15, 1957) the patient had further spiking temperature with sudden onset of sharp, cramping abdominal pain, chiefly left-sided, associated with local tenderness, and with persistent vomiting. Peristaltic sounds were diminished. Clinical jaundice was noted. Laboratory investigations at this stage showed a white blood cell count of 16,200 per cu. mm.; slight (1-plus) albuminuria; serum bilirubin, 3.2 mg. per cent; cephalin flocculation test, negative; thymol flocculation test, negative; thymol turbidity test, 4.0 units; blood amylase, 21 Russell units (normal, 8 to 18 units); serum glutamic-oxaloacetic transaminase, 65 units (normal, 8 to 40 units); blood non-protein nitrogen, 43 mg. per cent; serum electrolytes, normal;

stools, liquid with recent red blood; abdominal x-ray, suggestion of free air within the peritoneal cavity.

Laparotomy was therefore undertaken on February 16, 1957, nine hours after the acute onset of abdominal pain, the preoperative diagnosis being perforated duodenal ulcer. The findings were as follows: The gallbladder was necrotic and the adjacent tissues bile-stained. On gross examination, the liver, stomach and duodenum were normal. The small bowel from the ligament of Treitz through the ileocecal valve was ischemic, gray in color with mottled black areas primarily on the antimesenteric border. No pulses were present in the superior mesenteric, inferior mesenteric, left gastric or splenic arteries, and the spleen was unusually small. The pancreas was avascular and largely necrotic. The superior mesenteric artery was isolated and opened. Old brown clot, atheromatous material and thickened intima were withdrawn, and a good pulsatile blood flow secured. This was followed by rapid return of circulation to the small bowel. The gray areas became bright red, and peristaltic waves reappeared. The poor circulation to the colon was unchanged. Cholecystostomy and, for purposes of future direct inspection of the large bowel, transverse colostomy were performed.

Laparotomy was again carried out on February 18, 1957, to permit direct inspection of the suspect areas of bowel. Both small and large bowel appeared viable, although some dark (not black) areas persisted. The appendix was acutely inflamed and gangrenous, and was removed.

Following this, the patient's condition gradually improved. His abdominal pain diminished and his fever gradually resolved, although he had some wound sepsis. His colostomy opened on the second postoperative day. Serum electrolytes remained within normal limits, and on February 22, serum bilirubin was 2.6 mg. per cent, blood non-protein nitrogen 50 mg. per cent, and serum alkaline phosphatase 15.9 Bodansky units. Repeated stool cultures grew no pathogenic organisms. On March 1, electrocardiography showed that the patient had had a silent posterior myocardial infarct since his initial tracing.

As a result of our experiences with Case 1, detailed studies of intestinal absorption were made before the patient's discharge from the hospital. During this study period, from March 21 to April 25, the patient showed further steady improvement. He was ambulant and took a liberal diet, his weight increasing from 57.0 Kg. to 60.3 Kg.

Radiologic examination of the alimentary tract on March 27, 1957, showed a deformed duodenal cap consistent with old duodenal ulcer, but no frank ulcer crater. Transit of barium through the small bowel was slow and peristalsis much diminished. The jejunum was widened, and the mucosal pattern irregular throughout the small intestine.

The patient was discharged from the hospital feeling well on April 25, 1957. A further x-ray examina-

tion on May 2 showed the appearances to be improved, although the upper jejunum was widened and showed diminished peristalsis.

He was admitted a second time for closure of his colostomy on July 24, 1957. At operation it was found that the descending colon was pale and thickened, with a well-defined stricture just above the sigmoid colon. A side-to-side colocolostomy was performed to bypass this and closure of the transverse colostomy deferred.

When last seen on April 16, 1958, the patient was well and again at work.

*Metabolic Studies. Hematologic data:* Peripheral blood examination showed only a mild normochromic anemia which required a transfusion of 1,000 ml. After the initial episode stools were persistently guaiac-negative.

Plasma pepsinogen was slightly increased to 510 units per ml., consistent with his past history of duodenal ulcer. Vitamin B<sub>12</sub> absorption by the Schilling test was normal, the twenty-four-hour excretion of <sup>58</sup>Co-B<sub>12</sub> being 6.8 per cent. The serum iron was low, being only 40% per cent. These tests were all performed five to six weeks postoperatively.

*Carbohydrate metabolism:* Despite the patient's known pancreatic damage, there was no clinical or laboratory evidence of diabetes mellitus. An oral glucose tolerance test on March 22, 1957, showed a fasting blood sugar of 83 mg. per cent with a maximal rise to 130 mg. per cent at one and a half hours and a rapid fall towards fasting levels. The d-xylose test demonstrated impaired carbohydrate absorption on two occasions. This was initially severe (0.5 gm. on March 12, 1957) but on April 24 appeared to improve slightly.

*Fat metabolism:* Stool microscopy showed a moderate excess of split fats and soaps. The serum cholesterol was within the lower normal range, the serum carotene was 0.4 to 0.7 mcg. per ml. Lipid absorption tests (Table I) were well below normal.

Fat balance studies confirmed this evidence of faulty absorption of fats. These were carried out in six periods (Table II), during two of which the patient received oral pancreatic extract (pancreatin,<sup>®</sup> 45 gm. daily). In all periods the fecal fat greatly exceeded the normal upper limit of 5 per cent of the fat intake.

The results indicate that the patient had steatorrhea. That this was largely due to malabsorption and not to pancreatic deficiency is suggested by the finding that the fecal fats were largely split, and during the balance studies steatorrhea persisted even when pancreatic extracts were given in full dosage.

*Protein metabolism:* There was a significant shift in the protein pattern during the period of study, a fall in serum albumin to 2.9 gm. per cent and a rise in globulin to 4.1 gm. per cent. Paper electrophoresis on March 26 showed a considerable increase in  $\gamma$ -globulin and a slight increase in  $\alpha_2$ -globulin. These changes had reversed to normal levels by July 29, 1957.

Nitrogen balance studies were performed together

with the fat balances already recorded. The fecal nitrogen for the five balance periods was 2.0, 2.5, 2.4, 3.2 and 2.5 gm. per day, the upper limit of normal in this laboratory being 2 gm. per day.

*Other data:* Plasma electrolyte values were normal throughout the period of study. The serum calcium was 9.0 mg. per cent and inorganic phosphorus 4.1 mg. per cent on March 26. The blood non-protein nitrogen remained elevated (49 mg. per cent in July).

The patient during the period of observation showed the chemical changes associated with liver damage. The serum protein changes have been mentioned. The jaundice disappeared within two weeks, but an alkaline phosphatase of about 8 Bodansky units and a 3-plus cephalin flocculation test were noted in mid-April. Bromsulphalein retention was 12.1 per cent on March 26. The prothrombin concentration remained at 100 per cent.

*Comment:* This case is strikingly similar to Case 1, and again there is strong presumptive evidence that intestinal malabsorption resulted from temporary occlusion of the intestinal arterial supply. This was patent during the patient's first operation on January 30, and occluded by thrombus at operation February 16, eighteen days later. Precise timing of the duration of occlusion is difficult, but it would appear to have been slightly less than twelve hours.

The arterial occlusion in this instance was due, not to embolus, but to thrombosis occurring in arteries already considerably affected by atheromas. For this reason it was, paradoxically, more extensive but produced less ultimate upset of alimentary function. The occlusion affected the celiac axis and both superior and inferior mesenteric arteries, and the resulting ischemia affected liver, gallbladder, pancreas, and small and large intestines. Hepatic anoxia was shown by the change in liver function tests that followed occlusion and slowly returned towards normal over the succeeding months. The gallbladder became necrotic and was drained. The pancreas at operation was avascular and partly necrotic. The colon later developed a typical ischemic stricture. Small bowel ischemia was shown directly at operation and later by the development of radiological changes and a defect of absorption. As in Case 1, this malabsorption involved fat, carbohydrate and protein; but not, in this case, vitamin B<sub>12</sub>.

#### COMMENTS

While there has been considerable speculation concerning the role of vascular factors in intes-

nal absorption and small bowel disease, little precise information is available. The earlier literature has been summarized by Klein [12]. While it is known that a major mesenteric vessel may undergo complete obliteration without causing symptoms, this is considered to be rare. However, Shaw and Green [13] have reported a case of atheroma of the superior mesenteric artery in which the intestinal arterial supply was almost entirely through the coeliac axis and inferior mesenteric artery. In this patient, operative ligation of the inferior mesenteric artery in the course of colonic surgery led to extensive infarction of both small and large intestine.

More recently, attention has turned to the clinical sequelae of mesenteric vascular disease. Since the early descriptions of "intermittent mesenteric claudication" or "abdominal angina," additional case reports have appeared sporadically [14,15]. Joske [16,17] has described a syndrome of generalized vascular disease associated with atrophic gastritis and pancreatitis. He attributes these latter to progressive mesenteric ischemia. Shaw and Maynard have reported a patient with the malabsorption syndrome due to chronic superior mesenteric artery occlusion [2].

Less attention has been paid to the late results of acute mesenteric vascular occlusion and it is generally stated that acute occlusion of a major mesenteric artery leads to infarction and general peritonitis unless bowel resection is possible. However, Hawkins [18] has described a case in which mesenteric infarction led to tubular stenosis of the jejunum with clinical steatorrhea and radiologic appearances resembling those seen in Crohn's disease. There have been several reports of localized intestinal strictures following temporary incarceration of the bowel in a hernia or after embolism of the smaller mesenteric vessels [10,19,20].

The present cases of extensive acute occlusion of the mesenteric vessels with survival after arterotomy appear to be unique. There can be little doubt that the clinical, radiologic and metabolic findings in these cases resulted from temporary mesenteric ischemia. Survival of the second patient may well have been due to the pre-existing atheroma so that some collateral circulation had developed before the final catastrophe.

It is noteworthy that such an acute and limited episode of ischemia produced prolonged failure of absorption. Regeneration of the ali-

mentary mucosal cells is rapid. Leblond and Stevens [27] have shown that in the albino rat the average life of intestinal epithelial cells is less than two days. Nevertheless in these patients malabsorption continued for weeks and months, although there was evidence in each case of some progressive improvement. It would seem therefore that two factors are involved. Initial anoxia would result in mucosal cell necrosis with (presumably) rapid regeneration. This may be followed by a slower phase apparently due to faulty organization of the new cells into a functioning tissue.

## SUMMARY

Two patients are reported, each of whom suffered an occlusion of the superior mesenteric artery which was successfully treated by arteriotomy without resection of intestine. In each case this episode of ischemia was followed by a prolonged malabsorptive state. It is suggested that mesenteric vascular disease be considered in the differential diagnosis of the malabsorption syndrome.

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# Steatorrhea Associated with Ulcerogenic Tumor of the Pancreas\*

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IN 1956 Zollinger and Ellison [1] described a group of patients representing a newly recognized clinical entity. These patients presented the triad of peptic ulcerations of the stomach and small bowel, marked gastric hypersecretion, and non-insulin-producing islet cell tumors of the pancreas. In a subsequent comprehensive review Ellison [2] described the clinical and pathologic characteristics in twenty-four cases collected from the literature.

Inasmuch as malabsorption has not to our knowledge been described in association with this syndrome, it is considered of interest to present a patient in whom steatorrhea was the dominant feature, and who was followed for nearly five years and treated for the "malabsorption syndrome" before the true nature of his disease became apparent.

## CASE REPORT

The patient was a fifty-three year old chemist who was first admitted to the Massachusetts General Hospital in July, 1955, with a three-year history of diarrhea, nausea, abdominal pain and weight loss. In 1938 he had undergone an appendectomy for acute appendicitis; following this he had complained of some pain in the mid-epigastrium and right upper quadrant, which was investigated at another clinic. After the demonstration of cholelithiasis, a cholecystectomy had been performed in 1940 with good symptomatic relief. It is of interest that on two occasions during this investigation he had been found to have "achlorhydria." The patient had then remained relatively well until 1952 when he noted the onset of anorexia, nausea and postprandial diarrhea which consisted of large, soft, foul-smelling stools. Subsequently he experienced dull mid-epigastric pain, which was most prominent following meals, and he began to vomit small amounts of clear acid-tasting liquid. His physician documented steatorrhea and performed a roentgenographic study of the upper gastrointestinal tract and small bowel, which demonstrated a "deficiency pattern." Following this the

most likely diagnosis was considered to be "non-tropical sprue." In 1954 a bilateral inguinal herniorrhaphy had been performed, at which time a small bowel biopsy specimen had been obtained and interpreted as being normal. Glossitis had developed and the patient had been treated with multi-vitamins, folic acid and vitamin B<sub>12</sub>. On this therapy his tongue had cleared, but the other symptoms had become progressively worse. His weight had fallen from an initial level of 197 pounds to a low of 114 pounds at the time of his first admission to this hospital.

On examination he was a thin, wasted person who appeared chronically ill. The remainder of the examination, except for old abdominal scars and minimal clubbing of fingers and toes, revealed no abnormalities. Initial laboratory studies revealed the hemoglobin, white blood count and differential, urinalysis and sedimentation rate to be normal. Stools were guaiac-negative but on microscopic examination showed markedly increased amounts of split fats. A three-day intake-output study showed that he excreted 32.5 per cent of ingested fat (29.3 gm./day). Fecal nitrogen was normal (1.7 gm./day). Serum electrolytes were normal as were serum calcium, phosphorus and alkaline phosphatase. Other normal values of interest were those for serum proteins, serum iron and prothrombin time.

Gastric aspiration was productive of fluid containing 93 clinical units of free acid per 100 ml. without histamine. Duodenal drainage revealed an acid fluid of pH 4.5 (normal 6.0 to 7.5) with 1,200 Russell units of amylase per ml. and 10 per cent tryptic activity. It was believed that the low enzyme levels were a reflection of the low pH and indicated acid inactivation. Oral glucose tolerance tests gave a slightly diabetic-type curve on one occasion and a normal curve on a second; the result of an intravenous test was normal. Other tests of absorption revealed a serum carotene of 0.3 units/ml. (normal 1 to 3 units/ml.) and a flat vitamin A tolerance curve. The d-xylose absorption test was at the lower limits of normal, 4.5 gm. excretion in five hours [3].

Roentgenograms of the upper gastrointestinal tract and small bowel showed prominent, coarse folds in the stomach, duodenum and entire small bowel.

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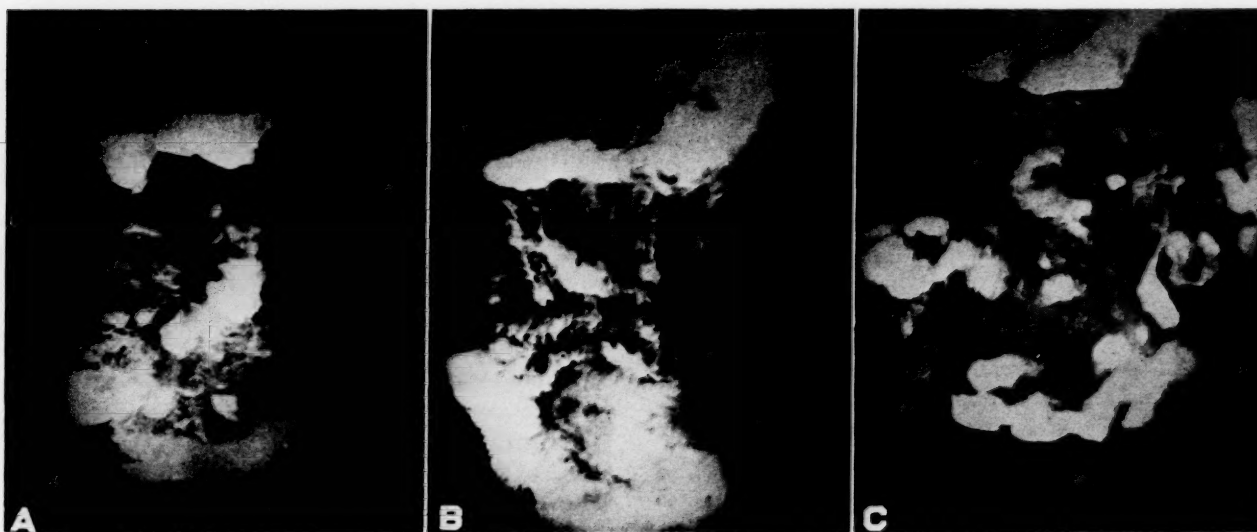


FIG. 1. Roentgenograms of upper gastrointestinal tract and small bowel with aqueous barium sulphate suspension, demonstrating: (A) gastric and small intestinal hypersecretion with fluid levels; (B) thickened folds in stomach and small bowel; and (C) segmentation and flocculation of barium characteristic of the "deficiency pattern."

There was an increased amount of fluid in the stomach. In the small intestine the barium progressed slowly through dilated loops. These changes were interpreted as consistent with a diagnosis of non-tropical sprue. (Fig. 1.) It was believed that despite certain inconsistencies the best diagnosis was indeed that of non-tropical sprue, and the patient was discharged after three weeks having been instructed to follow a program which included the ingestion of prednisone, 40 mg. daily, potassium chloride, testosterone and supplemental vitamins.

His response to this regimen was equivocal, with some improvement in appetite but little change in diarrhea or cramps. He was therefore given a trial period on a gluten-free diet and later with pancreatic extract (20 gm. per day, U.S.P.); there was no benefit. In January, 1956, he began to have nausea in the morning with vomiting of approximately 300 ml. of acid-tasting fluid. At about this time he noted edema of the ankles, although the serum albumin levels remained normal. Studies during this period contributed little, repeat roentgenograms revealed the same gastric and small intestinal patterns. One finding of interest was that his plasma pepsinogen, an indirect measurement of basal gastric secretory activity, was 1,500 units (normal 200 to 450 units). This was the highest value recorded in our laboratory and is unlikely to be only a reflection of corticosteroid therapy. Of interest is that at no time did the patient complain of ulcer-type pain, and repeated roentgenologic examinations never revealed peptic ulceration.

His course continued down-hill and there was some increase in abdominal pain. He was readmitted to this hospital on January 16, 1957. Gastrosocopy at this time showed markedly increased secretion and thick, ragged gastric folds. A biopsy specimen re-

vealed glands containing numerous parietal cells, but it was considered normal.

In view of the uncertainty as to the nature of his "malabsorption syndrome" and because of his failure to respond to therapy an exploratory examination was carried out on January 28, 1957. \* Operation disclosed a tumor which appeared to replace most of the body of the pancreas, and one obvious metastasis in the liver. The stomach and small bowel appeared normal on gross examination without external signs of ulceration. Biopsy specimens were taken of the pancreatic tumor, metastasis, stomach and jejunum, and the abdomen was closed. The operative diagnosis was metastatic adenocarcinoma of the pancreas.

The surprising microscopic finding was that the tumor was a highly differentiated one, "composed of nests and plump strands of uniform cells with eosinophilic cytoplasm and vesicular nuclei. Reticulum stains showed septa between cords of cells and some reticulum about each cell." The pathologic diagnosis was "consistent with carcinoma of the islets of Langerhans with metastasis to liver." Gastric and jejunal biopsy specimens were normal; there was no evidence of sprue in the latter.

In retrospect it seemed likely that this tumor was an extremely slowly growing example of the ulcerogenic type described by Zollinger and Ellison. In this instance, instead of producing a picture dominated by recurrent peptic ulceration, the resultant gastric and perhaps intestinal hypersecretion had produced a picture in which malabsorption was the initial and predominant feature.

During the patient's postoperative convalescent period certain other studies were made. More detailed gastric secretory tests confirmed the clinical impres-

\* Operation performed by Dr. Marshall K. Bartlett.

sion of extreme hypersecretion.\* Basal gastric secretion was 605 ml. per hour with an average pH of 0.98 and free acid of 104 clinical units per 100 ml. This was apparently a maximum level of secretion and did not increase significantly after infusion of peptone broth or administration of histamine. The possibility of adenomas in the pituitary or parathyroids, as found in other cases of the Zollinger-Ellison syndrome, was investigated; the results were negative. On the hypothesis that the tumor might be secreting some substance which stimulated gastric secretion via a humoral route and could be detected by the presence of abnormal protein or amino acids, the following studies were performed but findings were normal: serum electrophoresis (paper and Tiselius methods), electrophoresis of concentrated urine, and chromatography of plasma dialysate and urine.

In the hope that the bulk of this slowly growing tumor would be sufficiently localized to excise, thus presumably ameliorating the patient's symptoms, it was decided to reexplore. On March 8, 1957 a second laparotomy revealed that the tumor was inoperable in that it encircled the superior mesenteric artery and vein. Postoperatively the patient's condition deteriorated slowly, nausea, vomiting and abdominal pain persisting. He was discharged on March 30, 1957, and managed at home until readmission for terminal care on April 22; he died on May 19, 1957.

Postmortem examination confirmed the previous operative findings of a large pancreatic tumor, which replaced the entire organ except for a small portion of the head. At this time numerous metastatic nodules were seen in the liver. The additional finding of interest was that of several small (0.3 to 0.5 cm.) peptic ulcerations in the jejunum; one of which had perforated with some localized peritonitis, there were no other endocrine adenomas. The microscopic appearance of the tumor was identical with that of the previous biopsy specimen. Gastric and small intestinal mucosa in the non-ulcerated areas showed only postmortem autolysis.

#### COMMENTS

Zollinger and Ellison in their description of the syndrome associated with ulcerogenic tumors of the pancreas have defined a clinical entity which seems to be of increasing importance as general awareness of the problem spreads and more cases are discovered. In the patients described to date the important clinical problem has been recurrent peptic ulceration, and we are becoming alert for these tumors as possible etiologic factors in patients with strong ulcer diatheses. In a few instances watery diarrhea has been prominent, and occasionally hypokalemia has resulted [4]. It is of interest that these tumors may be associated with a different

\* Kindly performed by Dr. William R. Waddell

clinical picture in which malabsorption with steatorrhea is the initial and dominant feature.

The relationship between these tumors and other clinical features of the syndrome remains unclear. The assumption has been made that the tumors in some way produce the gastric hypersecretion, perhaps by way of a humoral intermediate. It should be emphasized that a causal relationship has not as yet been demonstrated and that perhaps the hypersecretion, the pancreatic tumor and the other endocrine adenomas so frequently seen are all the result of another undefined stimulus. We have recently seen another patient who presented the classical clinical picture of this disorder, gastric hypersecretion, diarrhea, and repeated ulceration throughout the upper small bowel. Repeated laparotomies failed to reveal any pancreatic tumor, and when she died despite all surgical efforts to control her virulent peptic disease, no tumor could be found.

The cause of the steatorrhea in this instance is likewise unclear, but from the data at hand perhaps three hypotheses might be offered. First it is possible that the extreme hyperchlorhydria resulted in a low duodenal pH and thereby inactivated the pancreatic enzymes. At pH 4.5 pancreatic digestive enzymes are almost completely inactivated, and it is reasonable to suppose that a duodenal pH in this range might result in a relative pancreatic insufficiency. It could also account for the fact that an active pancreatin preparation in large dosage did not produce any clinical benefit. Secondly the abnormal roentgenographic pattern suggesting small bowel hypersecretion, while non-specific, might nevertheless indicate that the stimulus to gastric hypersecretion had an effect on the intestinal mucosa as well. Finally, it is probable that a terminal mechanism was simply that of pancreatic insufficiency due to replacement of exocrine tissue by tumor. It is unlikely, however, that this third mechanism was operative early in the course when the tumor was small. Had this been the case, one might have found increased fecal nitrogen or neutral fat in the stools, and a response to administration of pancreatin would be expected.

Inasmuch as the "malabsorption syndrome" remains to a large extent a descriptive diagnosis in which varied etiologic factors may play a role, it may be of importance to consider pancreatic islet cell tumor in the occasional case. It would perhaps be helpful to include a study of gastric

secretory volume in the investigation of certain cases and to explore the pancreas carefully in those demonstrating an abnormally high level of secretion.

In the literature we have found two other reported cases which might represent unrecognized examples or variants of this syndrome. In a paper by Beres et al. [5] mention is made of a patient who manifested both steatorrhea and gastric hyperchlorhydria. It was of considerable interest to learn [6] that in this patient a jejunal ulcer subsequently developed and an exploratory examination was performed. At this operation no pancreatic tumor was found, but at a second laparotomy a small tumor in the second portion of the duodenum was resected. Histologically this tumor has been difficult to classify, but its appearance is thought to be compatible with a pancreatic islet cell origin. It is of further interest that resection of this tumor did not affect the patient's gastric hypersecretion. In 1949 Machella et al. [7] described a patient with gastric hyperchlorhydria, jejunal ulceration and hypoproteinemia. An acid duodenal and jejunal pH was noted, and it was the opinion of the authors that this pH change was responsible for the hypoproteinemia. At that time the relationship between jejunal ulceration, gastric hypersecretion and pancreatic tumor had not been described, but surgical exploration failed to disclose any pancreatic abnormality. This patient has been well for nine years following total gastrectomy [8]. Despite the presumed absence of a pancreatic tumor and with probable malabsorption of protein rather than fat, it may nonetheless be reasonable to suggest that this patient represents a related mechanism of pathologic physiology.

## SUMMARY

A patient with ulcerogenic tumor of the pancreas is reported in whom malabsorption was the dominant clinical feature. The other characteristics of the Zollinger-Ellison syndrome, gastric hypersecretion and peptic ulceration, were not noted until after the tumor had been found at exploration, the ulcerations developing only terminally. Possible relationships between the gastric hypersecretion and malabsorption are discussed. It is believed that pancreatic islet cell tumor of the non-insulin-secreting type should be considered as a possible etiologic or associated factor in the occasional patient with the "malabsorption syndrome."

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# Clinical and Histological Observations in Fatal Non-tropical Sprue\*

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NON-TROPICAL sprue continues to be a disease of unknown etiology characterized by evidence of intestinal malabsorption. Study of its pathogenesis has been hampered by the scanty evidence of any destructive pathological lesion [1]. There are said to be no specific changes in the gastrointestinal tract on gross or histological examination in idiopathic primary sprue [2]. Opportunities to obtain tissue for study in patients with primary sprue are infrequent and the rapidity of small intestinal autolysis in postmortem material has further interfered with histological investigation of the disorder.

Adlersberg and Schein in 1947 described the postmortem findings in six patients with non-tropical sprue and commented on the lack of any specific pathological lesion [2]. Cooke et al. also commented upon the "absence of relevant pathological findings at autopsy in 9 patients" [3]. Milanes et al. described a jejunal biopsy performed in a patient with tropical sprue and reviewed the few pre-existing microscopic reports [4]. More recent information has been added by Paulley who obtained operative jejunal biopsies from four patients with idiopathic steatorrhea [5] and Butterworth and Perez-Santiago who studied jejunal tissue obtained at operation in six patients with tropical sprue [6]. Development of the "Shiner" intestinal biopsy tube has made it possible to obtain material for examination without resorting to laparotomy, and such specimens have already yielded knowledge of mucosal changes in diseases of malabsorption [7-9]. Himes, Gabriel and Adlersberg have recorded what are probably the first postmortem studies of patients with non-tropical sprue who have received prolonged corticosteroid therapy [10,11].

The observations to be reported concern a patient with severe malabsorption syndrome observed for two and a half years. Various types

of treatment including a gluten-free diet, and administration of corticosteroids failed to produce sustained improvement. Tissue was fortunately obtained both during life and at autopsy in this patient, providing an opportunity to study the histological changes associated with an unusually severe case of non-tropical sprue.

## CASE REPORT

R. A. (SMH No. 172797), a fifty-one year old white married farmer, was admitted to the Strong Memorial Hospital on December 20, 1954, with a chief complaint of eight to ten bowel movements a day for one month. Four years prior to admission he had been studied at another hospital because of weight loss and loose stools. He weighed 36 kg. at that time. Studies there were said to be within normal limits except for a "deficiency pattern" of the small bowel demonstrated by x-ray examination. He improved slowly on supportive therapy and gained weight up to 68 kg. The patient's only other complaints were excessive flatus and mild abdominal pain in the left upper quadrant. There was no history suggesting celiac disease in childhood. He had never noted soreness of the tongue. The patient had a marked personality disorder and for many years, numerous domestic and emotional difficulties had occurred. The family history was non-contributory. His father was a full-blooded American Indian.

The temperature on admission was 38.7°C., pulse 72, respirations 22, blood pressure 95/55 mm. Hg, and weight 51 kg. The patient was well developed but extremely thin and appeared chronically ill. There was no abnormal skin pigmentation. The bowel sounds were hyperactive. The liver and spleen were not palpable.

The hematocrit was 44 per cent (Wintrobe) and the hemoglobin 14.6 gm. per cent. The white blood count was 13,500 per cu. mm. A differential count showed 32 per cent polymorphonuclears, 1 per cent band forms, 53 per cent lymphocytes, 9 per cent monocytes, and 4 per cent eosinophils. The red blood cells showed slight anisocytosis. A reticulocyte count was 1.1 per cent. Urinalysis was within normal limits.

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The stools were bulky, yellow and foul. Numerous fat droplets were noted on staining with Sudan III and analysis of a four-day stool specimen showed that fat comprised 50 per cent of the dry weight of the stool. Cultures revealed no enteric pathogens and no parasites or ova were present. Repeated tests for occult blood were negative.

The total serum protein was 5.1 gm. per cent, albumin 2.7 gm. per cent, globulin 2.4 gm. per cent, serum calcium 8.8 mg. per cent, serum phosphorus 3.0 mg. per cent, cholesterol 118 mg. per cent, cholesterol-cephalin flocculation test negative, and thymol turbidity test 0.5 MacLagen units. The prothrombin concentration was 40 per cent of normal. An oral glucose tolerance test (50 gm.) gave the following results: fasting blood sugar 81 mg. per cent, a half hour 83 mg. per cent, one hour 80 mg. per cent, two hours 62 mg. per cent, three hours 85 mg. per cent, and four hours 77 mg. per cent. The serum carotene was 50  $\mu$ g. per 100 cc. (normal 75 to 150). A fasting blood vitamin A level was 20 units per 100 cc. (normal 15 to 40). Four and a half hours after a large dose of vitamin A was given orally the level was 45 units per 100 cc. (normal 100 to 250).

Material obtained by duodenal intubation showed normal enzymatic activity. A gastric analysis showed free acid after histamine stimulation. Tuberculin skin tests were negative in a dilution of 1:100. A postero-anterior film of the chest revealed no abnormalities. X-ray series of the upper gastrointestinal tract showed a markedly abnormal small bowel pattern with puddling and clumping of the barium. A barium enema was within normal limits except for a redundant sigmoid colon.

During the first week in the hospital, several unexplained temperature elevations occurred. He had no fever at any time thereafter. The patient was given a gluten-free diet, oral vitamins and antispasmodics. Diarrhea subsided and he gained 4 kg. of weight. The white blood count rose to 15,000 per cu. mm. with a persistent lymphocytosis of 50 to 60 per cent. Posterior cervical lymphadenopathy developed, as did slight ankle edema. He was discharged from the hospital on February 9, 1955.

The patient was seen in the medical outpatient department on February 18, 1955. He felt very weak and had gained no further weight. Little improvement had occurred following exclusion of gluten from the diet. Cortisone therapy in a dosage of 100 mg. a day orally was started at this time. He was instructed to continue with his diet and avoid free salt and excessive amounts of fat. Potassium salts were given by mouth. The results of blood studies made just prior to the institution of cortisone therapy were as follows: hematocrit 50 per cent, hemoglobin 16.9 gm. per cent, white blood cell count 22,450 per cu. mm., polymorphonuclears 56 per cent, band forms 6 per cent, lymphocytes 35 per cent (many of them atypical), and eosinophils 2 per cent. The serum

sodium and potassium were normal. The serum calcium was 8.8 mg. per cent, phosphorus 4.4 mg. per cent, total protein 6.1 gm. per cent, albumin 2.7 gm. per cent, and globulin 3.4 gm. per cent.

After one week of treatment with cortisone the patient stated that he felt much better. The appetite had improved and he was having only one formed stool a day. The white blood count was 36,750 per cu. mm. with no change in the differential. After two weeks of cortisone therapy he had gained 5 kg. and "felt fine." There was no edema. The white blood cell count was 21,000 per cu. mm., total serum protein 5.8 gm. per cent, albumin 3.2 gm. per cent, globulin 2.6 gm. per cent, calcium 8.9 mg. per cent, and phosphorus 4.0 mg. per cent. A stool analysis at this time showed 32 per cent fat by dry weight.

After three weeks he seemed to have improved considerably and the dosage of cortisone was reduced to 75 mg. a day. After four weeks on cortisone the patient weighed 63.8 kg. and improvement continued. However, following the fifth week his family reported bizarre behavior and he was readmitted to the hospital on March 25, 1955, because of what was probably a psychotic episode precipitated by cortisone. Cortisone was gradually reduced and finally discontinued on April 4, 1955.

He was then discharged from the hospital and was seen again in the Medical Clinic on April 22, 1955. He weighed 58 kg. and said he felt "rotten." Diarrhea to the extent of six loose stools a day had recurred. During the next week his weight dropped to 54 kg. and he was readmitted to the hospital. For the next five weeks his course was one of progressive deterioration, despite continuation of the gluten-free diet, intramuscular vitamin B<sub>12</sub>, folic acid and other supportive measures. His weight fell to 49 kg. and severe diarrhea persisted. The white blood count continued to be between 15,000 and 20,000 per cu. mm. The hematocrit and hemoglobin remained normal. A bone marrow examination showed only lymphocytic infiltration. The total serum protein fell to 4.1 gm. per cent, albumin 1.6 gm. per cent, globulin 2.5 gm. per cent. Hypocalcemia of 4 to 6 mg. per cent developed, accompanied by tetany. The fat content of the stool was 41 per cent of dry weight. A deficiency pattern of the small intestine was again demonstrated by x-ray.

An exploratory laparotomy was performed on June 8, 1955, to exclude regional enteritis, intestinal lipodystrophy, lymphoma or other primary disease causing the absorptive defect. At operation the small bowel was dilated and edematous. The mesentery was also edematous and contained a number of enlarged lymph nodes. Both bowel and mesentery were easily traumatized and ecchymoses appeared with minimal manipulation. The liver and spleen appeared normal and no other abnormalities were found. Biopsy specimens were taken from the jejunum at a point 18 inches below the ligament of Trietz. Biopsy specimens were also obtained from the liver and several

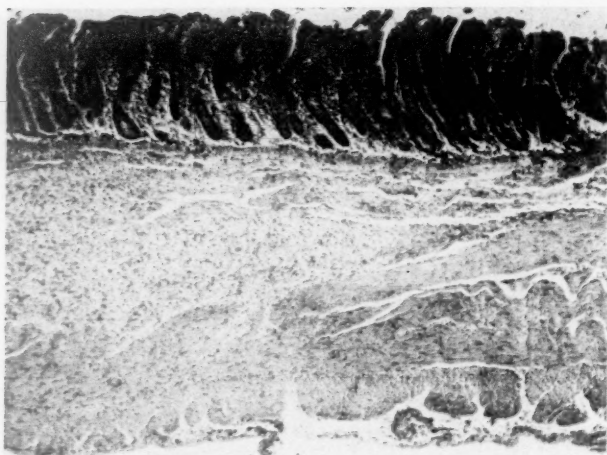


FIG. 1. Photomicrograph of the operative jejunal biopsy showing thinning of the mucosa with shortening and thickening of the villi, many of which appear to adhere to one another. Inflammatory and fibrotic changes are present in the submucosa and to a lesser extent in the muscular coats of the bowel wall. Hematoxylin and eosin.

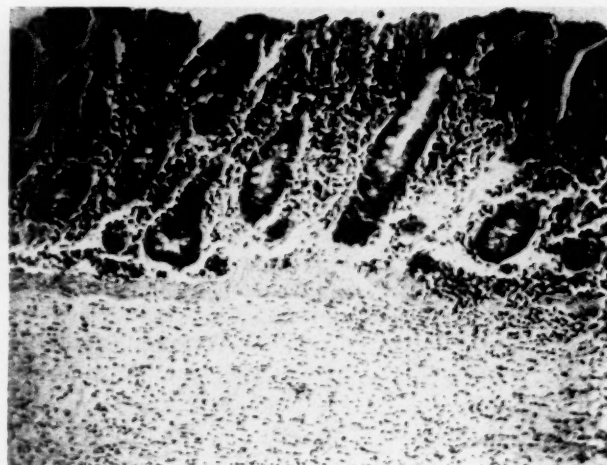


FIG. 2. Operative jejunal biopsy showing abnormal villi and infiltration of the lamina propria with chronic inflammatory cells. Hematoxylin and eosin.

lymph nodes were removed from the mesentery and transverse mesocolon.

Microscopic examination of sections taken from the jejunum showed a marked variation from the normal appearance. (Figs. 1 and 2.) None of the usual plicae were present in any of the sections. The mucosal tissue appeared thinned, with crowding together of the villi which were short, thickened and in many instances fused together. Very few Paneth cells were present in the crypts. There were a moderate number of mitotic figures predominantly in the lower half of each crypt. There appeared to be a crowding together of the epithelial cells lining the upper third of each crypt and the cells on the mucosal surface toward the lumen were particularly crowded. This seemed to suggest a loss of the normal shedding phenomenon of the intestinal mucosa described by Hooper [12].

In the lamina propria there was a moderately extensive infiltration with chronic inflammatory cells predominantly lymphocytes and plasma cells as well as a sprinkling of histiocytes and a few scattered eosinophils and neutrophils. The muscularis mucosa was normal except for a few tiny areas in which it was disrupted by accumulations of chronic inflammatory cells. In the submucosa large areas were present consisting of closely packed, tiny collagen fibrils giving evidence of rather extensive fibrosis. The submucosa was moderately heavily infiltrated with lymphocytes, plasma cells and histiocytes. In one area of the fibrotic submucosa containing several large cells of Meissner's plexus, the fibrous tissue and inflammatory component appeared as a plaque-like structure. The small arteries and veins traversing this area did not appear abnormal and there was no evidence of inflammation in their walls.

The muscular coats were of normal thickness with a

relatively normal Auerbach's plexus between the two. A few plasma cells and wandering mononuclear cells were seen in the inner muscular layer and a few similar cells were located between the two muscle coats. The cytoplasm of the outer longitudinal muscle coat was more abundant than usual although the thickness of the layer was not excessive. In addition a considerable number of the muscle cells contained a light greenish brown pigment which usually occupied a vacuolated area in a paranuclear position. This pigment had the same general appearance as that which is seen in a similar position in the cardiac muscle fibers. It is presumably a lipochrome pigment of the "wear and tear" variety (hemofuscin) and its significance is not known. This hemofuscinosis of the muscular coats has been noted by others and is described in the recent symposium on malabsorption syndrome [5,11]. The serosa did not appear abnormal.

The liver biopsy demonstrated a severe degree of fatty metamorphosis and the early changes of portal cirrhosis. The lymph nodes revealed very inconspicuous germinal centers and sinusoids. Most of the nodal tissue consisted of small and medium-sized lymphocytes. These appeared to be definitely hyperplastic and obscured the normal architecture of the node. However, sufficient trabeculae and reticuloendothelial cells could be seen to exclude any form of lymphoma. A few non-specific lipophages were present within the pulp of the node tissue. The sections were interpreted as showing a moderately severe lymphocytic hyperplasia of a reactive type, non-specific in nature.

Special stains of various tissues for amyloid material and periodic acid-Schiff stain for mucopolysaccharides were negative.

Cortisone therapy, 100 mg. a day intramuscularly, was reinstituted during the preoperative period. The patient withstood the procedure satisfactorily. However, despite steroids, vitamins, parenteral vitamin D and a gluten-free diet, the patient's condi-

tion continued to go downhill. There was persistent diarrhea, extreme emaciation (weight 43 kg.), edema, hypoproteinemia and hypocalcemia. The hematocrit slowly dropped to 32 per cent. White blood count elevations to 30,000 per cu. mm. occurred periodically. A relative lymphocytosis persisted and bone marrow examination again showed only lymphocytic infiltration. A serum iron determination gave a value of 19 gammas per cent. (Lower limit of normal 100 gammas per cent.) Repeated tests for occult blood in the stools were negative. Hypocalcemic tetany repeatedly occurred.

The patient had an acute anterior myocardial infarction on August 7, 1955. He surprisingly made a good recovery.

Transient improvement occurred during the first two weeks of September, 1955. A relapse developed during the third week in October, 1955 with severe diarrhea and hypocalcemic tetany. At this time measurement of his urine volumes demonstrated a so-called nocturnal diuresis. (Table I.) Cortisone was replaced by prednisone, 30 mg. a day orally. During the next two months he steadily improved. The serum calcium which had been between 4 and 6 mg. per cent slowly rose to 10 mg. per cent. His weight increased to 62 kg. and the serum albumin rose to 4.2 mg. per cent. All edema disappeared. The prothrombin concentration rose from 30 per cent to 100 per cent of normal. He had no diarrhea but fat still comprised 50 per cent of the dry weight of the stool. The hematocrit rose to 42 per cent. A leukocytosis in the range of 15,000 per cu. mm. with 40 per cent lymphocytes persisted.

On December 23, 1955, the patient was discharged to a nursing home in another part of New York State. During the eight-month period of hospitalization he had received 14 gm. of cortisone and 1.5 gm. of prednisone.

The patient continued to do fairly well for two months but severe diarrhea and weight loss then recurred. In April, 1956 he again became mentally disturbed and threatened to burn the nursing home and kill himself. This necessitated admission to a state mental institution on April 14, 1956. He weighed 50 kg. at this time and was having severe diarrhea. The blood pressure was 108/80 mm. Hg. The hemoglobin was 13.7 gm. per cent and the white blood count 16,850 per cu. mm. A differential count showed 52 per cent neutrophils, 44 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. Diarrhea persisted and edema of the lower extremities developed. On June 16, 1956, signs of cardiac decompensation occurred and he died on June 17, 1956.

Postmortem examination was performed the same day. The body was extremely emaciated and there was marked edema of the lower extremities.

The heart was small and weighed 200 gm. On the anterior surface of the left ventricle there was a raised, greyish fibrosed area representing the previous myocardial infarction. On cut section the myocardium

was brownish red in color. There was evidence of scarring in the anterior wall of the left ventricle. The valves were membranous with small atheromatous plaques. The coronary vessels were patent. The right lung weighed 650 gm. and the left 520 gm. There was marked congestion and hyperemia of the lower lobes.

TABLE I  
URINE VOLUME STUDIES

7 A.M. 1/13/55 to 12 P.M.	
1/13/55.....	700 cc. (41 cc./hour)
12 P.M. 1/13/55 to 7 A.M.	
1/14/55.....	1500 cc. (214 cc./hour)
7 P.M. 10/3/55 to 7 A.M.	
10/4/55.....	2800 cc.
7 A.M. 10/4/55 to 7 P.M.	
10/4/55.....	400 cc.
7 P.M. 10/4/55 to 7 A.M.	
10/5/55.....	2000 cc.
7 A.M. 10/5/55 to 7 P.M.	
10/5/55.....	475 cc.
7 P.M. 10/5/55 to 7 A.M.	
10/6/55.....	900 cc.
7 A.M. 10/6/55 to 7 P.M.	
10/6/55.....	310 cc.
7 P.M. 10/6/55 to 7 A.M.	
10/7/55.....	1100 cc.

The liver weighed 1,850 gm. It was more yellow than usual but otherwise appeared normal. The gall-bladder and extrahepatic bile ducts were normal. The pancreas weighed 50 gm. and was smaller than usual. The adrenals were grossly normal.

No fluid or adhesions were present in the abdominal cavity. The intestines were distended and edematous. The stomach revealed no abnormalities. The mucous membrane of the small bowel was flattened, injected and edematous. No gross ulcerations were present. The colon showed loss of the normal haustrations and the entire mucous membrane was injected but not ulcerated.

Sections of the small intestine and mesenteric lymph nodes were sent to the New York State Department of Health, Division of Laboratories and Research, and were loaned to us for examination. Six sections taken from the small bowel were available for study. There was a moderate degree of autolysis of the mucosa which was thinner than normal in the part that remained. The most striking abnormality was severe edema of the submucosa and in some portions of the serosa. Dilated lymphatic and venous channels were present in the submucosa, but little inflammatory component was present. Moderate lymphocytic and plasma cell infiltration of the lamina propria was noted and some cells, particularly those near the tips of the villi, contained black granules in their cytoplasm which were presumably the fragments of nuclear debris. The muscle coats showed no significant ab-

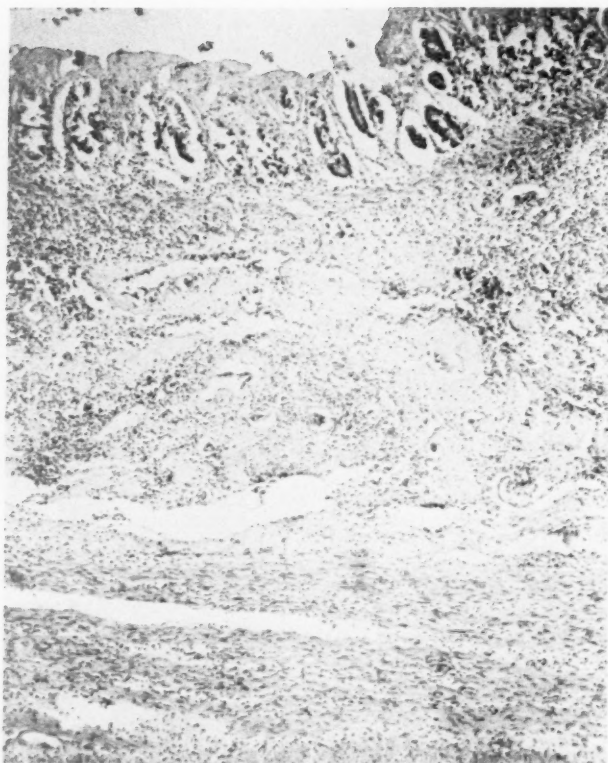


FIG. 3. Photomicrograph of section from jejunum taken at autopsy. Autolysis has damaged the mucosa but the villi still appear abnormal. Inflammatory changes in the bowel wall are more pronounced than in the operative specimens. Hematoxylin and eosin.

normality, except for edema and mild infiltration with chronic inflammatory cells in the regions of the myenteric plexus. The ganglion cells of this plexus appeared normal, but the nerve fibers were somewhat swollen.

One section appeared different from the others in that all the layers were heavily infiltrated by acute and chronic inflammatory cells. (Fig. 3.) The inflammatory infiltrate was most marked in the submucosa where lymphocytes, plasma cells, histiocytes and many neutrophils and degenerating leukocytes of indeterminate type were present. Similar cells were also located in all other coats of the bowel wall. The lamina propria was edematous. In a few areas there were flask-shaped depressions in the mucosal surface which penetrated through the muscularis mucosa. In these regions there was a more conspicuous acute inflammatory infiltrate with a great many degenerating leukocytes. Numerous long, rod-shaped bacilli were present in these areas which were believed to be microscopic mucosal ulcerations.

Between the inflammatory cells in the thickened submucosa there was an abundant pale pink material which had a distinctly fibrillar character under high power. This substance was birefringent when viewed with polarized light, indicating that it was of collagen nature. In this section there were fewer inflammatory

cells in the muscular coats, with some concentration of inflammatory cells around the myenteric plexus.

Many of the longitudinal muscle fibers contained greenish brown pigment granules similar to those seen in the biopsy specimen. These pigment granules were not seen in other sections from the autopsy material where the inflammatory infiltrate was less significant.

Sections from the mesenteric lymph nodes differed in appearance from those seen in the biopsy material. There was no evidence of germinal center activity and the sinusoids were widely dilated. The nodal tissue appeared hypoplastic with the possible exception of the reticuloendothelial cells in a few of the nodes. In some areas there appeared to be a striking leukoerythrophagocytosis and in these regions a large number of scattered long, rod-shaped bacteria were present. Some of these bacteria were within the cytoplasm of phagocytic cells, while others were scattered free in the spaces between the cells. In no area was there any inflammatory reaction.

#### DISCUSSION OF CLINICAL FEATURES

As has been pointed out by Adlersberg [10], sprue is a syndrome rather than a disease, with clinical and laboratory findings reflecting malabsorption from the gastrointestinal tract. The diagnosis of primary sprue rests on the exclusion of other pathological states which may produce similar manifestations.

On clinical grounds the diagnosis of idiopathic sprue in the patient described in this report seems justified on the basis of the following findings: severe malnutrition; severe and persistent diarrhea; hypoproteinemia; hypocalcemia with tetany; hypoprothrombinemia; steatorrhea; low serum carotene levels and impaired absorption of vitamin A; low glucose tolerance curves; nocturnal diuresis [13]; the roentgenographic appearance of the small intestine; and normal enzymatic activity of the duodenal juice.

The operative and autopsy findings revealed no evidence of any of the diseases which have been known to produce the sprue syndrome (secondary sprue); intestinal lipodystrophy, lymphosarcoma, Hodgkin's disease, amyloidosis and granulomatous jejunoileitis.

Anemia, a frequent manifestation of sprue [14-16], was not a striking feature of this case, which is surprising in view of the marked interference with most phases of intestinal absorption. At one time the hematocrit slowly decreased to 32 per cent. There were no evidences of bleeding or hemolysis during this period and the serum iron level was extremely low. For these reasons it

seems possible that absorption of iron was at least temporarily impaired.

The elevated white blood cell count, which ranged from 13,000 to 30,000 per cu. mm. during the period of observation, is a finding not often described in non-tropical sprue [14,15]. Estren comments that it occurs in less than 10 per cent of the cases [16]. Leukocytosis was present prior to the institution of cortisone therapy. A relative lymphocytosis, up to 60 per cent, was frequently present. The spleen was never enlarged and two bone marrow examinations showed only lymphocytic infiltration. The explanation for these blood findings remains a subject for speculation, but they may have represented a response to the pathological process in the small bowel.

Emotional disturbances were a prominent feature of this patient's clinical course. He presented a variety of behavioral patterns including prominent hostility, passive aggressiveness and frankly psychotic episodes. The psychiatric opinion was that basically he was an example of schizoid character formation. Although psychic factors are not stressed in most current descriptions of non-tropical sprue, many of the early writers commented upon the frequency of mental symptoms such as depression, paranoia and neurasthenia. Among 100 patients with idiopathic steatorrhea, Cooke et al. observed two patients who had marked mental symptoms. Their behavior was described as "querulous and fractious" [3]. Paulley has reported that emotional factors influence the onset and relapses of idiopathic steatorrhea [5]. Our patient in all probability had pre-existing psychiatric problems, which were aggravated by the stress of a severe and chronic illness responding poorly to treatment. Cortisone seemed to precipitate psychotic behavior on at least one occasion, but mental abnormalities were present during all phases of his disease.

Although the role of adrenocortical hormones in intestinal absorption and in the etiology of sprue has not been established, the clinical response to corticosteroids of patients refractory to other types of treatment has been excellent [17-24]. Adlersberg has treated thirty-four patients with refractory sprue with prolonged courses of ACTH, cortisone, hydrocortisone and, more recently, prednisone with good results [23]. Our patient responded poorly to conventional therapy including a gluten-free diet, vitamin B<sub>12</sub> and folic acid. Cortisone administra-

tion initially produced convincing evidence of improvement but was discontinued when the patient became emotionally disturbed. Just prior to the exploratory laparotomy, cortisone was reinstituted by the parenteral route primarily as protection against adrenal insufficiency. It was continued postoperatively, at first by intramuscular injection and then orally for four months during which time it seemed to do little in promoting the processes of intestinal absorption. When prednisone was substituted for cortisone, improvement began and continued for the next two months. This was manifested by weight gain and marked subjective improvement as well as a rise in serum albumin and serum calcium and a return of the prothrombin concentration to normal levels. Steatorrhea, however, persisted.

Despite this favorable trend, a recurrence of all his problems developed two months after leaving the hospital and progressed to a fatal conclusion.

It was difficult in this patient to differentiate between spontaneous remissions of the disease process and a therapeutic response to corticosteroids. While the initial response to cortisone was good, and favorable results followed the administration of prednisone, long periods occurred during which cortisone was ineffective in alleviating the severe manifestations of malabsorption which eventually proved to be fatal. Certainly the dramatic and sustained improvement observed by us [24] and others [17-23] following administration of corticosteroids to patients with refractory sprue was not attained. This suggests that rarely there are patients with severe malabsorption in whom even this mode of treatment may be ineffective.

#### DISCUSSION OF HISTOLOGICAL FINDINGS

For many years there have been conflicting opinions regarding the pathologic changes in the small bowel of patients with sprue [6]. Observations by several independent groups during the past few years oppose the formerly held view that the small intestine is histologically normal in sprue [5-9,11]. Himes and Adlersberg have studied histological material from fifteen patients with non-tropical sprue, eleven at post-mortem examination and four in whom jejunal biopsies were obtained via the Shiner tube [9]. The gross changes which they observed included thinning and dilatation of the wall

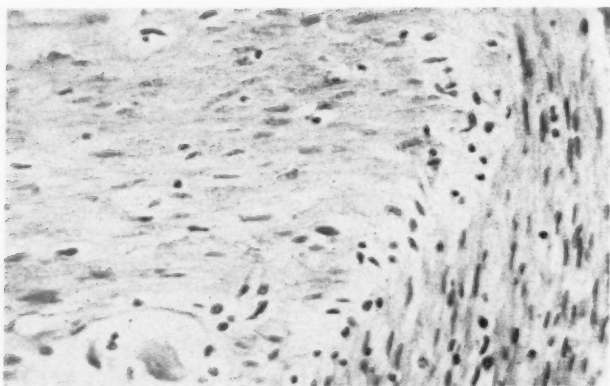


FIG. 4. Granular pigment within the muscle cells of the jejunal wall, most heavily deposited in the outer longitudinal layer.

of the small bowel with atrophy and flattening of the mucosal pattern. Microscopic examination of the jejunum showed the villi to be blunted and clubbed with a tendency to stick together. A cellular exudate, including many plasma cells, was present in the lamina propria. Culver et al., using surgical as well as Shiner tube biopsy of the jejunum in patients with non-tropical sprue, described the villi as being broad and flat-topped, rather than thin and feathery as they normally should be [8]. In addition, they noted that the usual columnar epithelium had been replaced by flat cuboidal epithelial cells many of which had undergone vacuolization. In the lamina propria, edema, cellular infiltration and increased connective tissue were present. Paulley observed edema, inflammation and broadened villi in operative jejunal biopsies from four patients with idiopathic steatorrhea [5]. Shiner found "mucosal, chiefly villous atrophy" to be the characteristic histopathologic defect in tube intestinal biopsies from seventeen patients with non-tropical sprue [7].

In regard to tropical sprue, Butterworth and Perez-Santiago obtained operative jejunal biopsies from six Puerto Ricans suffering from this condition: "every specimen revealed edema, infiltration of the lamina propria with chronic inflammatory cells and abnormally broad villi. Thinning of the mucosa was not a prominent feature. Five of the six specimens exhibited inflammatory vacuolation (sic) and thinning of the columnar layer itself" [6]. These findings correspond to those previously recorded by Milanes in a patient with tropical sprue, except that he observed thinning of the entire mucosal layer [4].

#### FINDINGS IN SPECIMENS OBTAINED AT SURGERY

The histological changes in the jejunum found in our patient correspond in many ways to those noted by the aforementioned observers in both tropical and non-tropical sprue. Thinning of the mucosa with short, thickened fused villi was one of the most prominent features. It has been suggested that these alterations in the villi result in a decrease in the absorptive surface of the small intestine, which could be a factor in producing malabsorption [6]. Hyaline material overlying the tips of the villi, such as was described by Schein in one patient, was not seen [25].

Another finding was what appeared to be at least a partial loss of the normal shedding or extrusion process of the small intestinal epithelium. The rate of cell turnover of the intestinal mucosa has been studied, morphologically, by Hooper [12]. He believes that cell turnover in an epithelium is an inherent property rather than a repair process induced by trauma, but that "the rate of turnover may be altered by a number of factors (eg. hormones) as well as factors of the external environment." Study of the sections in our patient suggest that the normal rate of cell turnover may have been defective, suggesting another morphologic abnormality in disorders of intestinal absorption.

In the lamina propria a considerable cellular infiltrate was present, corresponding with the findings of other observers in patients with non-tropical sprue. The submucosa also showed infiltration with chronic inflammatory cells as well as rather extensive fibrosis. Submucosal changes were more marked in this case than in the findings described by others [6,8,9]. Whether or not these structural changes actually interfered with the processes of intestinal absorption is a matter for speculation.

The muscular coats of the small intestine did not appear particularly abnormal. The greenish brown pigment seen within many of the muscle cells may be of a lipochrome nature and represent a metabolic breakdown product. Its significance is unknown to us and others [5,11]. It is interesting to note that it was most heavily deposited in the outer longitudinal muscle layer in the biopsy specimen. (Fig. 4.)

Enlargement of the mesenteric lymph nodes was a prominent finding in our patient. Histological examination revealed a marked non-specific lymphocytic hyperplasia rather than any

definitive pathological process. The persistent peripheral lymphocytosis may have been a reflection of this increased lymphoid tissue activity, which in turn possibly resulted from the changes seen in the small intestine. Enlarged mesenteric lymph nodes have also been found by Adlersberg in patients with sprue [2,9,11]. However, the microscopic picture was one of "lymphadenitis" and an element of fibrosis with increased trabeculation was noted.

The severe degree of fatty metamorphosis as well as early cirrhotic changes seen in the liver biopsy undoubtedly reflected the extremely poor nutritional state of the patient and are in line with the findings of others in cases of malabsorption [9,11].

#### POSTMORTEM FINDINGS

The gross changes in the intestinal tract at autopsy consisted primarily of flattening and injection of the mucous membrane. No macroscopic ulcerations or bleeding areas were present.

Autolytic changes, which have been so troublesome in postmortem microscopic studies of the small bowel, as usual interfered with histological interpretation of the mucosal layer. However, it seemed definite that there was thinning of the mucosa. Again an infiltration of chronic inflammatory cells was present throughout the lamina propria. The marked edema of the submucosa, which was less extensive in other layers, may have been related to the general fluid retention noted at the time of the patient's death.

In general, the inflammatory reaction and fibrotic changes were similar or slightly more extensive than those seen in the biopsy specimens. In one section, microscopic ulcerations penetrating down through the muscularis mucosa were present, as were acute and chronic inflammatory cells which infiltrated the entire intestinal wall. Marked fibrosis was seen in the submucosa. Rod-shaped bacilli in the ulcers and mesenteric lymph nodes indicated bacterial invasion. Although these ulcerations could have been terminal in type, it is conceivable that the changes represented progression of the same process seen in the biopsy specimens.

In this regard it is of interest to allude to the report of Himes et al. in which are described the postmortem findings of a patient with non-tropical sprue who was given prolonged corticosteroid therapy; apparently the first such case

to be described [10]. This patient, a thirty-four year old man with refractory sprue, initially had a good response to hormone administration for a two-year period. There then developed recurrent episodes of abdominal pain and fever as well as bouts of severe gastrointestinal bleeding. During the last six months of his life corticosteroids produced no improvement. Autopsy showed thinning and dilatation of the walls of the small bowel, but the most striking feature was numerous ulcerations and erosions, some as wide as 3 cm., throughout the small intestine but most prominent in the jejunum. There was also a small bowel perforation and several areas of jejunum in which the wall was markedly thickened and reddened.

Microscopic examination showed mucosal ulcerations in many sections of the small bowel. In those areas of the bowel wall which were thickened, a diffuse cellular reaction consisting primarily of large mononuclear cells and lymphocytes was present. The mesenteric lymph nodes were almost completely replaced by fibrous tissue or hyaline-like material.

These authors could not exclude the possibility that the findings in the small bowel were secondary to prolonged cachexia and malnutrition. However, they considered it more likely that they represented structural changes associated with an unusual form of malabsorption. It was also suggested by them that corticosteroid therapy may have contributed to the picture because of "the propensity of these drugs in causing ulceration and perforation of the gastrointestinal tract." Neither the clinical or pathological findings in their patient resembled the cases of "ulcerous jejunoileitis with symptomatic sprue" described by Svartz and Nyman [26,27] in Sweden or the case of Faber et al. [28] in which enlarged mesenteric nodes were a prominent feature.

It is obvious that the findings in our patient were much less spectacular and severe than in the case of Himes et al. Definite interpretation of the histological picture is impossible at the present time and any specific conclusions regarding the tissue changes would be ill advised. It can be stated that abnormal findings compatible with non-tropical sprue were present in the small bowel at the time of operation. Administration of corticosteroids failed to alter these changes favorably and there was probably some progression of the pathological process despite hormonal therapy. As Culver has pointed out, there

does not seem to be a clear-cut correlation between the severity of anatomical alteration and the absorptive defect in patients with non-tropical sprue, suggesting that biochemical abnormalities of the intestinal mucosal cells are the primary factor in the pathogenesis of the sprue syndrome [8]. However, it seems reasonable to assume that fibrotic changes such as were noted in our patient are irreversible, and by the structural alterations produced in the small bowel interfere with the processes of absorption.

## SUMMARY

A case of severe malabsorption syndrome in a fifty-one year old man is described. Conventional therapy including a gluten-free diet was unsuccessful. Administration of corticosteroids failed to produce the sustained improvement which has often been observed in such patients. Operative biopsy of the jejunum showed mucosal thinning with fusion and thickening of the villi as well as crowding together of the epithelial cells lining the crypts. Infiltration with chronic inflammatory cells was noted in the lamina propria and submucosa and there was also a considerable degree of fibrosis. Fourteen months later at postmortem examination, following prolonged treatment with cortisone and prednisone, there had been little alteration in the pathological process and possibly some progression.

*Acknowledgment:* We wish to acknowledge the cooperation of Dr. Kenneth Keill, Director of the Willard State Hospital and the New York State Department of Health, Division of Laboratories and Research, who loaned us the histological material that was available. Dr. Victor W. Logan, Assistant Professor of Medicine, made many helpful suggestions in the preparation of this report.

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# A Case of "Chronic Mountain Sickness" in the United States\*

## *Clinical, Physiologic and Electrocardiographic Observations*

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CHRONIC mountain sickness (Monge's disease) is an illness observed in subjects residing at high altitudes, and characterized by the appearance of intolerance to the lowered oxygen tension in a previously acclimatized person. This results in the appearance of polycythemia and produces a group of symptoms resembling those seen in patients with true erythremia (easy fatigability, headache, paresthesias, "fullness"). Cyanosis deepens in time, and periods of unconsciousness, sometimes ending in deep coma, may occur. These abnormalities disappear when the patient moves to sea level.

Monge first described this syndrome, which he observed in residents of the Peruvian Andes, in 1925. In subsequent accounts [1-3] he termed it "chronic mountain sickness" and enumerated its rather protean manifestations. Physiologic observations on this state have been recorded in the literature by Talbott and Dill [4] and by Hurtado [5]. A more detailed analysis of cases observed in the Peruvian Andes has recently appeared [6]. The present study was prompted because we are unaware of reports of cases of chronic mountain sickness occurring in the North American continent, and at the time of our observations no detailed studies concerning the pathologic physiology of the syndrome had appeared in the American literature.

The relation between the appearance of polycythemia, arterial desaturation, and disturbances in alveolar ventilation is well known. The obvious aggravation of minor degrees of arterial desaturation in patients with impaired ventilation who move to moderate altitudes is a function of the shape of the oxygen dissociation curve [7]. The marked improvement in patients with

Monge's disease on moving to sea level certainly has its parallel in this country in subjects with ventilatory disturbances and "secondary polycythemia" moving from the intermountain region to the coast. It is tempting to assume as the cause for Monge's disease a specific acquired pulmonary dysfunction, which by itself may or may not be related to the altitude.

The following observations in a twenty-eight year old resident of the Colorado Rocky Mountains who had spent most of his life at an altitude of 10,000 feet (3,000 meters) are reported because it appears that he fulfills Monge's and Hurtado's criteria for chronic mountain sickness, although he lived at an altitude lower than has been associated with true Monge's disease. This was a patient with marked erythrocytosis and certain abnormalities involving the cardio-respiratory system in whom polycythemia disappeared on moving to sea level, but in whom some physiologic disturbances in cardiopulmonary function could still be demonstrated two years after he had become asymptomatic.

### METHODS

The patient was studied on three separate occasions by the same group in Salt Lake City and once in Los Angeles.\* Standard procedures were employed. Cardiac catheterization was used for the determination of cardiac output by means of oxygen consumption and arteriovenous oxygen difference. Systemic and pulmonary artery pressure were measured by means of optimally damped strain gauge systems (Statham). Pulmonary function studies were performed according to the technics described by Baldwin

\* We are indebted to Dr. Hurley Motley for the observations reported at sea level listed in Tables I to III.

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and her associates [8]. The pulmonary ventilation perfusion relationships and the resting diffusing capacity were estimated by the technics described by Riley and others [9,10]. Angiocardiograms were obtained by rapid injection of 70 per cent diodrast,<sup>®</sup> and the circulating blood volume was estimated from the dilution of Evans blue dye (T-1824) and the hematocrit values. Glomerular filtration rate and renal blood flow were estimated by Smith's technic. Since the latter determinations added little to the understanding of the physiologic mechanisms involved, no further reference is made to these procedures.

#### CASE REPORT

The patient, C. N., was born in Colorado Springs, Colorado (elevation 6,036 feet; 1,830 meters) on September 13, 1927. He had resided in Fairplay, Colorado, (elevation 9,950 feet; 3,015 meters) throughout his childhood and adolescence. He had left Fairplay in January, 1946, to enlist in the Marine Corps. Until his discharge in October, 1947, he had served at various stations at or close to sea level. Upon discharge from the Marine Corps he had returned to Fairplay and had secured work as a ranch hand.

Until the summer of 1948 the patient had enjoyed excellent health and could recall no significant illness or symptoms. At that time he began to notice easy fatigue and increased shortness of breath on exertion. Because these symptoms persisted and increased, he had consulted a physician in the fall of 1949. Albuminuria is said to have been found and after treatment with antibiotics the patient reported some improvement. During the autumn of 1950 his symptoms of shortness of breath and easy fatigability again became prominent. Because a second course of antibiotic treatment failed to produce symptomatic improvement, he had consulted another physician. A markedly elevated red blood count was found. Therefore, on May 7, 1951, he was admitted to the Grand Junction Veterans Administration Hospital. His only complaints were easy fatigability and dyspnea on exertion. He denied cough, sputum production, or exposure to any toxic substances.

Examination at this time\* showed a robust appearing young man with reddish blue coloration of the hands and face, distinct cyanosis of the lips and marked conjunctival injection. His temperature, pulse rate and blood pressure were all normal. Ophthalmoscopic examination showed dilated fundic veins that were intensely dark. The chest expanded normally. A few basal rales were heard on one occasion, but no other abnormal physical finding was elicited over the lungs. The second pulmonic heart sound was thought to be accentuated but examination of the heart was otherwise within normal limits. In the abdomen, the edge of the liver could be palpated two fingerbreadths below the costal margin. No other

abdominal organs or masses were felt. The spleen was not palpable. The remainder of the physical examination was unrevealing. There was no clubbing of the fingers or toes.

Laboratory examination showed a packed red blood cell volume of 81 per cent; hemoglobin, 22 gm. per 100 cc.; and red blood count, 10 million per cu. mm. The white count was 7,000 per cu. mm., with a normal differential count. The platelets were not increased in number. Examination of the urine showed proteinuria that varied from + to ++, and numerous hyaline casts. The blood urea nitrogen was 11.3 mg. per 100 cc. The basal metabolic rate was +29 per cent. A serologic test for syphilis was negative. During the next two weeks, 1,200 cc. of blood was removed by several phlebotomies. On May 23, 1951, he was transferred to the Veterans hospital in Salt Lake City, Utah (elevation, 4,800 feet; 1,460 meters) for further studies. At that time the physical examination was unchanged except that the liver was no longer palpable. The volume of packed red blood cells was 78 per cent on admission. Examination of the urine was normal. The blood uric acid was 8.4 mg. per 100 cc. and the total protein was 7.4 gm. per 100 cc. with albumin, 4.9; and globulin, 2.5 gm. per 100 cc.

Without specific treatment, the patient gradually improved and at the time of his discharge on June 8, 1951, the volume of packed red blood cells had decreased to 67 per cent. He returned to his home in Fairplay and to his previous employment (farming). About a month after returning home he noted the return of lassitude, easy fatiguability and disabling dyspnea. On November 9, 1951, he was readmitted to the hospital in Salt Lake City. Physical examination was unchanged except for tenderness over the first metatarsal on the dorsum of the left foot. Laboratory examination showed 23.8 gm. hemoglobin per 100 cc., the volume of packed red blood cells was 80 per cent, and the blood uric acid was 12.4 mg. per 100 cc. The urine was clear. No tophi were noted. On bedrest the tenderness in his foot disappeared. His blood uric acid later during this admission was found to have decreased to 3.3 mg. per 100 cc. On the basis of the history and physical findings, together with the radiologic, electrocardiographic and cardiorespiratory function studies, a diagnosis of an illness similar to chronic mountain sickness (Monge's disease) was made and the patient was advised to change his residence to sea level.

Late in January, 1952 he moved to Los Angeles (elevation 275 feet). All symptoms disappeared shortly after his arrival there. Within six weeks the rubor and cyanosis, which had been apparent to the patient and his associates, was no longer noticed. Analysis of his blood on May 26, 1952, showed the volume of packed red blood cells to be 46 per cent, with 16.8 gm. hemoglobin per 100 cc. He has remained asymptomatic, has secured full time employment, and up to now (1957) has had no limitation of activity.

\* We are indebted to Dr. Stanley Crosbie for this report.

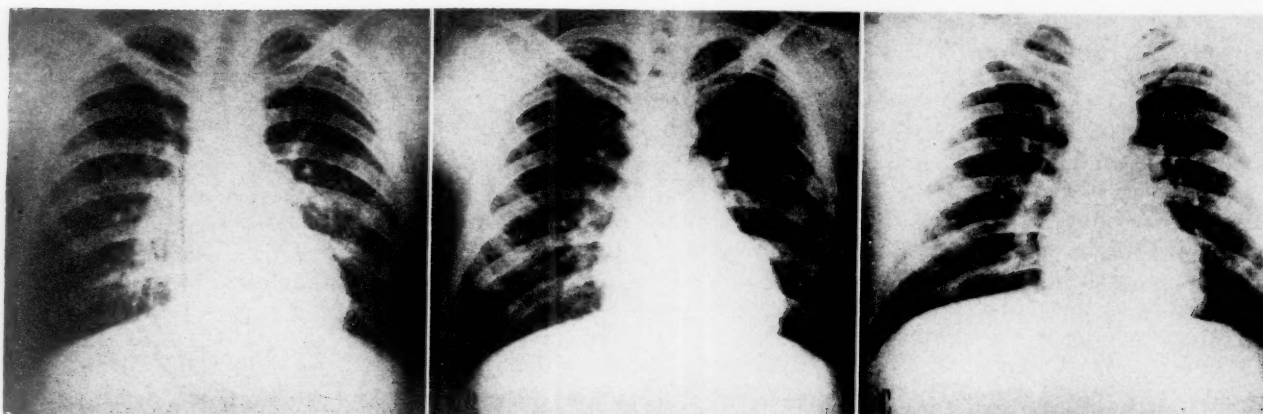


FIG. 1. Posteroanterior views of chest. A, obtained on May 24, 1951, B, on January 12, 1952 and C, on March 12, 1954. The patient became asymptomatic during the interval between (B) and (C).

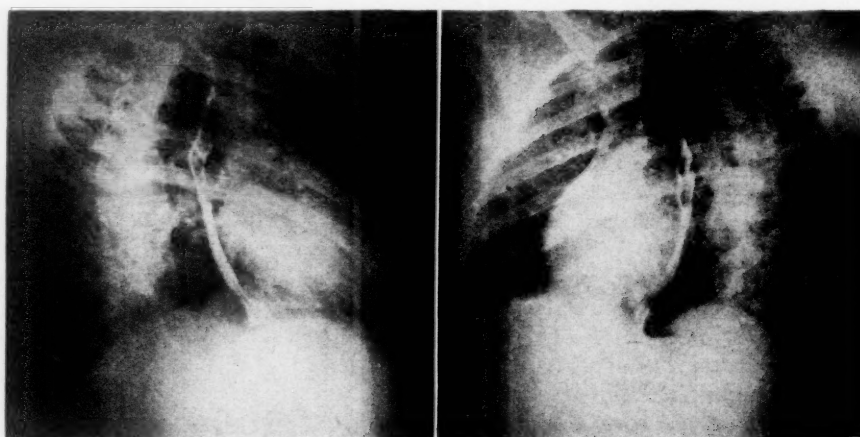


FIG. 2. Right anterior oblique and left anterior oblique views obtained on November 13, 1951, at the time of the second study.

He returned to Salt Lake City briefly in May, 1954, for re-evaluation. Now, the only abnormal physical finding elicited was an accentuated second pulmonic heart sound. The volume of packed red blood cells was 50 per cent, the hemoglobin 16.6 gm. per 100 cu. mm.

#### SPECIAL EXAMINATIONS

**X-rays.** Six serial x-ray examinations of the chest were obtained between May, 1951 and March, 1954. In 1951 the films demonstrated accentuation of pulmonary vascular markings with evidence of vascular congestion but without specific chamber enlargement. The pulmonary artery segment was prominent. During January, 1952, at a time the hematocrit readings were 80 per cent, the right ventricle showed increased prominence in the left anterior oblique projection. A chest film obtained on March 12, 1954, showed no abnormalities. (Figs. 1 and 2.)

An angiocardigram performed on November 20, 1951, in the anteroposterior projection demonstrated slow emptying of contrast medium from the right side of the heart. The right ventricle did not appear enlarged. The main pulmonary artery and both its major branches were increased in size. There was no

evidence of a gross intracardiac defect or of an intra pulmonary aneurysm.

An abdominal film gave no evidence of an enlarged spleen. No bony abnormalities were demonstrated on films of the left foot and right ankle.

**Electrocardiograms.** (Figs. 3 to 6.) At the height of the illness marked rightward deviation of the largest QRS vectors occurred on the frontal plane, associated with an increase in R and delayed downstrokes in the right-sided chest leads, as well as a sharp terminal inversion of T in the conventional mid precordial leads. It is apparent that during the acute episode the resultant electromotive forces during excitation pointed forward and to the right, those associated with recovery backward and to the left, resulting in an abnormally small ventricular gradient and a wide spatial angle between QRS and T at the height of the illness. (Fig. 6.) It is of interest that these changes occurred with rather minor alterations in pulmonary artery pressure or pulmonary arteriolar resistance, and that the electrocardiographic changes regressed completely despite persistence of the somewhat abnormal values for resting pulmonary artery pressures and the changes in oxygen diffusion capacity. There is little

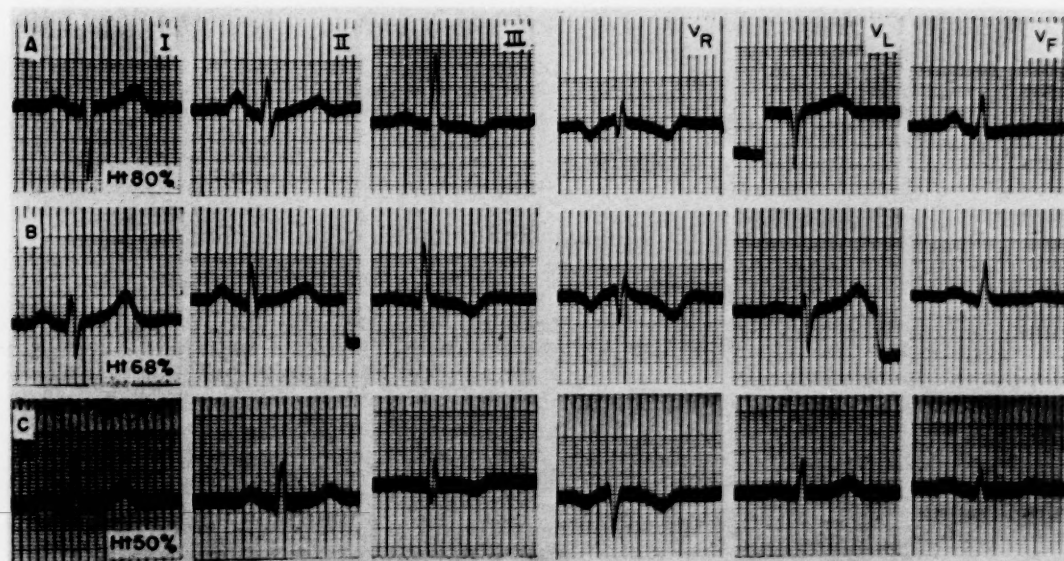


FIG. 3. Electrocardiograms. A, obtained on September 11, 1951, B, on June 3, 1951 and C, on March 12, 1954. Arranged in the receding order of values for packed red cell volumes. These frontal plane leads (I, II, III,  $V_R$ ,  $V_L$  and  $V_F$ ) demonstrated a shift in  $\alpha_F$  from  $+144^\circ$  (A) to  $+11.5^\circ$  (C), with a magnitude of the modal vector of from 1.82 mV (A) to 1.20 mV (C). (See Fig. 6.)

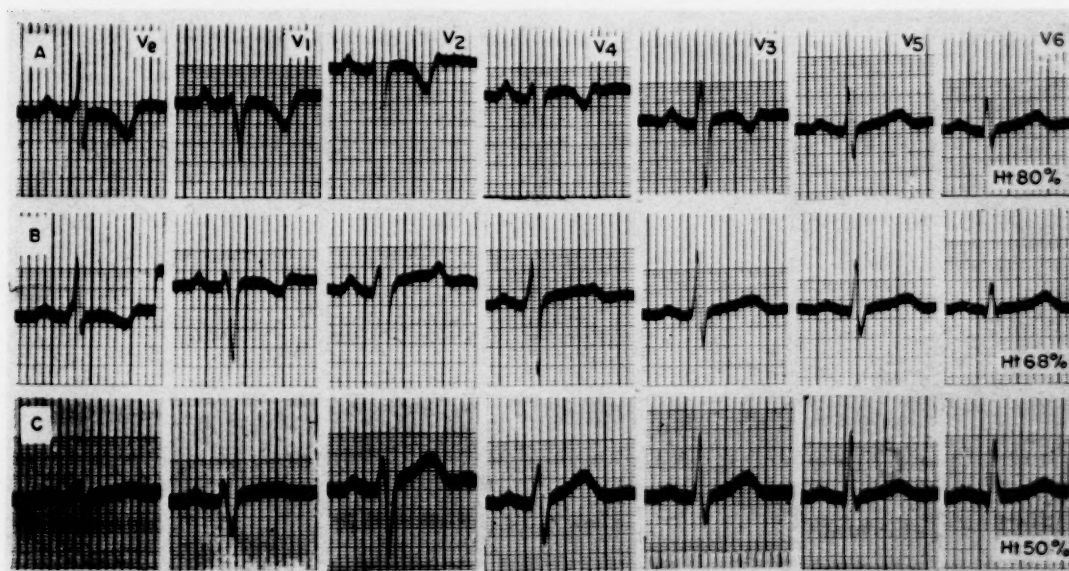


FIG. 4. Electrocardiograms (ensiform lead  $V_E$ , and standard precordial leads) arranged as in Fig. 3. Note tall R waves in A and B over ensiform lead, and gradually receding T wave inversion over the anterior precordium. A, and to some extent, B, are suggestive of right ventricular changes (enlargement and "strain").

question, however, that the changes are compatible with right ventricular "strain." In addition to the shift in direction of QRS and the change in the precordial electrocardiogram, the decrease in the magnitude of the ventricular gradient together with its apparent displacement posteriorly suggests that repolarization was delayed in the anterior (right ventricular) parts of the cardiac musculature: the gradient points always away from the region with the longest duration of excitation. The changes in direc-

tion and magnitude of QRS and T, and in the estimated ventricular gradient seem compatible with right ventricular "strain" or acute cor pulmonale. During hospitalization a gradual change toward normal occurred, and in 1954 an entirely normal electrocardiogram was recorded.

*Blood Gas Analyses, Hemodynamic and Respiratory Studies.* Details of the repeated studies performed on this patient are listed in Table I-v. The patient at all times demonstrated moderate to severe arterial

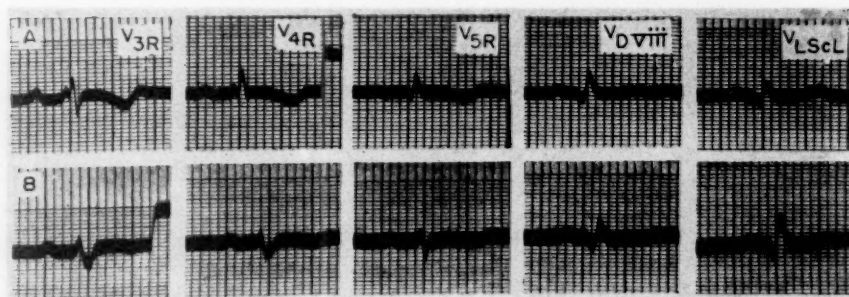


FIG. 5. Electrocardiograms. A, circumferential precordial leads in June, 1951 and B in March, 1954, displaying abnormal QRS changes over the right precordium compatible with right ventricular enlargement in A only. Leads to the left of the spine (D VIII) and in the left posterior scapular line (LSCL) have remained unchanged.

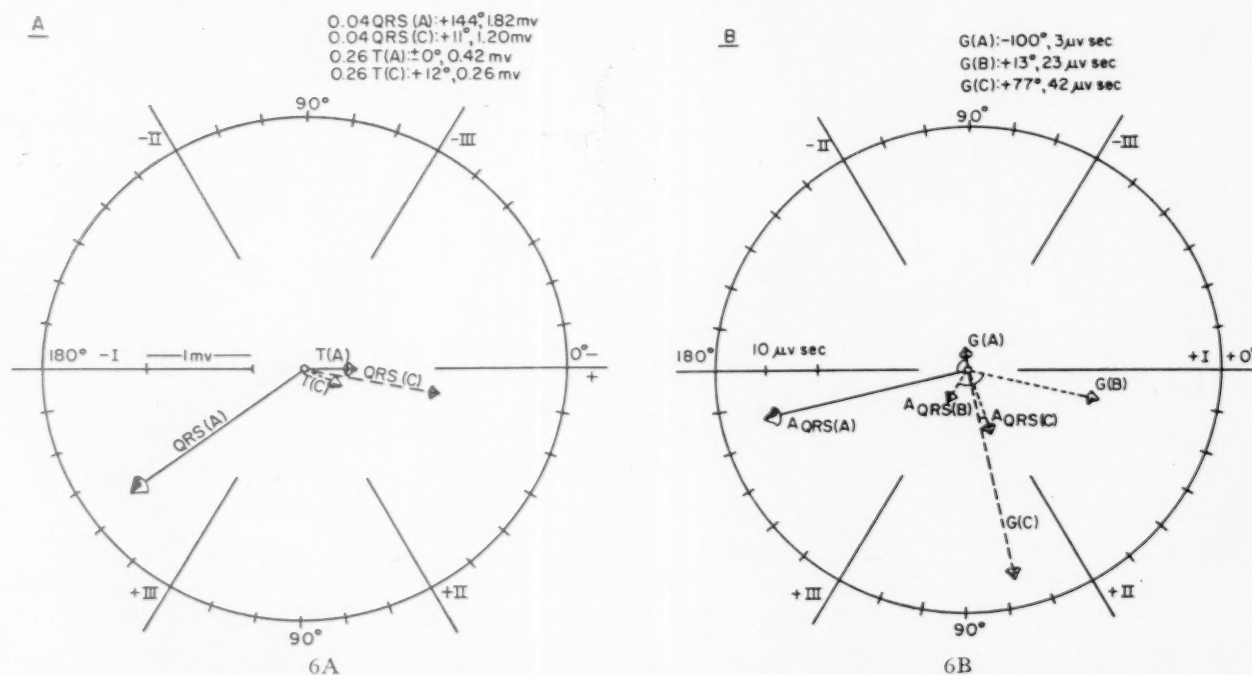


FIG. 6. Frontal plane analysis of tracings A and C shown in Fig. 3. Using circumferential precordial leads and null point analysis an approximate spatial position is also indicated. A, demonstrates QRS complexes at 0.04 second and T waves at 0.26 second after onset of ventricular excitation in I. B, illustrates the areas of QRS and G, the ventricular gradient, for all three tracings of Fig. 3 (A, B and C), with their approximate spatial arrangements. Note the increasing size of G with a gradual receding angle between G and AQRS. (Values were obtained from enlarged projections and planimetric measurements.)

oxygen unsaturation, which was not corrected at sea level. Even after he had resided in Los Angeles for two years and was asymptomatic, evidence of disturbed pulmonary gas exchange could be identified from the elevated venous admixture component and the reduced oxygen diffusing capacity at rest. (Table iv.) Pulmonary artery pressures and pulmonary arteriolar resistance were always slightly elevated.

#### COMMENTS

This patient had erythrocytes, right ventricular "strain," slight arterial oxygen unsaturation, moderately elevated pulmonary arterial pres-

TABLE I  
PHYSICAL CHARACTERISTICS, VOLUME OF PACKED  
RED CELLS AND HEMOGLOBIN CONCENTRATION

Date	Height (cm.)	Body Surface Area (m <sup>2</sup> )	Volume Packed Red Blood Cells (%)	Hemoglobin (gm./ 100 cc.)
May, 1951	174	1.90	76	23.3
November, 1951	174	1.92	78	22.6
May, 1952	174	2.03	46	16.8
March, 1953	174	2.03	50	16.8
March, 1954	174	2.10	50	16.6

TABLE II  
LUNG VOLUMES AND MAXIMUM BREATHING CAPACITY

Date	Vital Capacity (cc.)	Residual Volume (cc.)	Total Lung Capacity (cc.)	$\frac{\text{Residual Volume}}{\text{Total Lung Capacity}} \times 100$ (%)	Maximum Breathing Capacity (L./min.)
	<i>4275</i>	<i>1045</i>	<i>5320</i>	<i>20</i>	<i>140</i>
November, 1951.....	4500	.....	.....	...	...
March, 1953.....	4020	921	4941	19	114
March, 1954.....	4260	1045	5304	20	136

NOTE: Figures in italics represent normal values.

TABLE III  
VENTILATION AND RESPIRATORY GAS EXCHANGE

Date	Ventilation		Oxygen Consumption		Arterial Gas Values			
	$\dot{V}$ (BTPS) (L./min./m. <sup>2</sup> )		$\dot{V}_{O_2}$ (STPD) (ml./min./m. <sup>2</sup> )		Oxygen Saturation (S <sub>O<sub>2</sub></sub> %)		P <sub>aCO<sub>2</sub></sub> (mm. Hg)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
	<i>3.2</i>	<i>9.5*</i>	<i>126</i>	<i>600*</i>	<i>96</i>	<i>96†</i>	<i>39</i>	<i>39*</i>
	<i>4.9</i>	.....	<i>138</i>	.....	<i>93</i>	<i>93</i>	<i>32</i>	...
May, 1951..... (Salt Lake City)	4.0	5.2†	132	200†	73	71†	..	...
November, 1951..... (Salt Lake City)	4.7	5.9†	166	224†	87	86†	..	...
March, 1953†..... (Los Angeles)	2.9	11.1*	148	689*	90	91*	37	39*
March, 1954..... (Salt Lake City)	4.9	.....	129	188†	89	87†	38	...

NOTE: Figures in italics represent normal value; First line = sea level; second line = Salt Lake City.

\* "Standard" step exercise.

† "Steady state" leg raising exercise.

‡ By courtesy of Dr. Hurley Motley, Los Angeles, California.

tures, low normal cardiac output, slightly reduced pulmonary diffusing capacity and disturbance of the pulmonary ventilation-perfusion relationships. Clinically, he presented findings similar to those described in cases of chronic mountain sickness reported from South America [5,6].

Because of the arterial oxygen unsaturation and polycythemia, several diagnostic possibilities were considered and soon discarded. No evidence of intracardiac shunts was found by cardiac catheterization and by angiocardiography. Chronic pulmonary emphysema was not present. There was no reason to suspect multiple pulmonary emboli. His age, the absence

of leukocytosis, granulocytosis and splenic enlargement, the arterial unsaturation, elevated pulmonary resistance, and the response on moving to sea level ruled out the diagnosis of polycythemia vera. A large pulmonary arteriovenous aneurysm was not present but small terminal pulmonary arterial connections ("berry-aneurysms") could not be completely excluded. The response to changes in altitude would militate against any of these possibilities.

The response of the polycythemia to the higher oxygen tension of sea level establishes that it was secondary to hypoxia. That this abnormal hypoxia was caused by intrinsic and irreversible disease of the lung is evident from the persistence

TABLE IV  
VENTILATION-PERFUSION RELATIONSHIP AND RESTING OXYGEN DIFFUSING CAPACITY MARCH, 1954

Inspired Oxygen Concentration $PI_{O_2}$ (mm. Hg)	Alveolar Oxygen Concentration $P\dot{c}A_{O_2}$ (mm. Hg)	Arterial Oxygen Concentration $Pa_{O_2}$ (mm. Hg)	Resting Oxygen Diffusing Capacity $D_{O_2}$	Venous Admixture ( $\dot{Q}vA$ ) ( $\dot{Q}_T$ ) % of cardiac output	Dead Space Ventilation ( $\dot{V}_D$ ) ( $\dot{V}_T$ ) % of total ventilation
...	...	...	<i>15</i>	<i>&lt;6</i>	<i>&lt;30</i>
150	105	78	11	17	31
123	76	56			

NOTE: Figures in italics represent normal values.

TABLE V  
HEMODYNAMIC MEASUREMENTS

Date	Oxygen Consumption ( $\dot{V}_{O_2}$ ) (cc./min./m <sup>2</sup> )	Arterial Venous Oxygen Difference ( $Ca_{O_2}-C\bar{v}_{O_2}$ ) (cc./L.)	Cardiac Index (L./min./m <sup>2</sup> )	Pulmonary Artery Pressure (mm. Hg)		Pulmonary Arterial* Resistance (TAR) (units)
				Systolic/diastolic	Mean	
May, 1951.....	<i>126</i>	<i>39</i>	<i>2-4</i>	<i>25/10</i>	<i>15</i>	2.0
	136	47	2.7	44/18	27	7.0
	(200)	(51)	(3.6)	(59/26)	(37)	( 8.1)
November, 1951.....	166	45	3.8	46/14	25	4.5
	(224)	(47)	(4.8)	(95/43)	(60)	(11.0)
March, 1954.....	129	41	3.1	42/20	27	6.1
	(188)	(57)	(4.2)	(54/28)	(36)	( 8.8)

NOTE: Figures in italics represent normal values. Figures in parentheses were obtained during "steady state" leg raising exercise.

\* "Wedge" pressure 8 mm. Hg resistance values are given in units [7].

at sea level of arterial oxygen unsaturation, elevated pulmonary arterial pressure, slightly reduced diffusing capacity and pulmonary ventilation perfusion abnormalities. Without further information or access to histologic findings, one can only speculate on the etiology and nature of the pulmonary changes in this case. Hurtado [5] has suggested that these patients may have "fibrosclerotic" changes which cause a reduction in the oxygen diffusing capacity of the lung, somehow caused by exposure to the lowered oxygen concentration. An alternate explanation would seem to be that while at high altitudes, some diffuse disturbance at the alveolar-capillary junction or within the pulmonary vasculature develops coincidentally in these patients which causes a reduction in the apparent diffusing capacity and obvious ven-

tilation perfusion abnormalities. It is well known that such derangements are more apparent when the patient is exposed to a lower oxygen tension [7]. For this reason one may speculate from this case as to whether or not chronic mountain sickness in general may not be caused by such slight disturbances in respiratory gas exchange as would not be likely to cause signs or symptoms at sea level.

One interesting feature of this patient's illness was the electrocardiographic evidence of right ventricular hypertrophy and "strain" which was observed during the early part of his illness. These changes completely regressed to normal after he had resided at sea level. An unusual correlation existed between the electrocardiographic changes of right ventricular enlargement and the degree of polycythemia. It is

unlikely that this relationship was a direct one. Both abnormalities, it seems, depended on a third factor. The increase in the volume of packed red cells and the abnormalities in the electrocardiographic findings were most marked whenever the patient was admitted following a sojourn at high altitudes. The stimulus for increased erythropoiesis is associated with an average daily arterial unsaturation of 70 to 75 per cent [7]. The patient approached this value at rest at least on one occasion, and may have reached it at other times during heavy exercise or during sleep. That it was obviously associated with changes in the  $P_{O_2}$  of the inspired air demonstrates that the primary anomaly was concerned with the gas exchange mechanism, and that the pulmonary vascular changes presumably were secondary.

The pronounced transient electrocardiographic changes suggesting right ventricular overloading are not likely the result of changes in "viscosity" since patients with polycythemia vera and high packed red cell volumes usually give normal hemodynamic and electrocardiographic data [7]. Nor does anoxemia of the degree present here cause significant electrocardiographic changes. The observed increase in pulmonary resistance was not high enough to interfere appreciably with right ventricular function. (Table v.) However, severe pulmonary hypertension on exercise was observed on one occasion, at a time when the patient was quite ill (November, 1951). It seems reasonable to assume that at the height of the illness and at high altitudes, persistent pulmonary vasoconstriction with elevation of pulmonary artery pressure was present well in excess of what could be recorded, and that the relatively long periods at lower altitudes (May, 1951 and March, 1954) had already resulted in significant improvement in this respect. In November, 1951, (electrocardiogram A of Fig. 3), when the observed pressures were highest, cardiac catheterization was performed within a day after arrival from high altitudes, whereas the first observation (May, 1951) was obtained after several weeks of sojourn at lower levels (electrocardiogram B of Fig. 3). In the absence of demonstrable evidence of pulmonary emboli, the findings suggest reversible pulmonary vascular changes with right ventricular overloading ("strain") which

was already receding when the patient came under observation.

It seems clear that this patient, who presented many of the classic features of chronic mountain sickness, suffers from a mild form of lung disease which has persisted after the subject moved to low altitudes.

#### SUMMARY

1. A case of chronic mountain sickness is described in a resident of the Colorado Rocky Mountains. Clinical, electrocardiographic and cardiopulmonary physiologic studies are presented. Signs, symptoms and electrocardiographic abnormalities disappeared when the patient moved to sea level. However, evidence of persistent intrinsic, mild pulmonary disease could still be identified after he had resided at sea level for more than two years.

2. It is proposed that some cases of chronic mountain sickness may result from disturbances in respiratory gas exchange and altered ventilation-perfusion ratios on the basis of intrinsic pulmonary disease, too mild to cause signs or symptoms at sea level.

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# Idiopathic Hypoparathyroidism Presenting as a Psychosis and Complicated by Chlorpromazine Jaundice\*

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IDIOPATHIC hypoparathyroidism has been intensively studied and the criteria for its diagnosis well defined [1,2]. Among its clinical manifestations psychosis has been described, but perhaps has not been sufficiently emphasized. Indeed, the diagnosis of idiopathic hypoparathyroidism, in itself a rare disease, may be difficult or even inapparent when a psychological disturbance is the predominant manifestation or precedes other clinical signs such as tetany. This case, complicated by chlorpromazine jaundice, represented such a situation and afforded an opportunity to correlate psychological and electroencephalographic data with the clinical and biochemical changes of idiopathic hypoparathyroidism.

## CASE REPORT

This fifty-nine year old married woman (No. 417972) was referred to the psychiatric service of the University of Rochester Medical Center on June 21, 1956, because of increasing anxiety. During the preceding eight years she had been seen on several occasions by her local physician for hypertension and obesity. Several months before admission she became increasingly anxious and depressed, and noted constipation, insomnia and early morning awakening. In the month or two before admission she had the urge to be continually active, yet gave up church attendance, stopped caring for her home, and ceased preparing meals. Her husband reported some paranoid tendencies.

Three weeks before admission therapy with phenobarbital, chlorpromazine 25 mg. four times a day and reserpine 0.25 mg. four times a day was begun. Several days before admission she complained of generalized itching followed by yellow skin, dark urine, and "mustard-colored" stools. Chlorpromazine was stopped

but she continued to feel nervous and was referred for psychiatric admission.

The past history, although incomplete, revealed no contact with patients with hepatitis and no recent injections or venipunctures. She had "passed out in the heat" briefly a few days before admission. There had been no neck surgery.

On physical examination the blood pressure was 140/80 mm. Hg, pulse 80, respirations 16, and temperature 36.9°C. The patient was disoriented as to the date but not as to the place. She could not remember her birth date, but could name recent and incumbent American presidents. Subtraction was poorly performed. Occasionally she misinterpreted words. She cried frequently, was self-depreciatory, and complained of itching. The skin was dry, coarse and intensely jaundiced. There was moderate generalized obesity. The nails were normal. Pupils were reactive and the fundi revealed no abnormalities. The heart was minimally enlarged to percussion. No murmurs were heard. The lungs were clear. Liver and spleen were not palpable. Deep tendon reflexes were hyporeactive but the neurological examination was otherwise normal. The Chvostek sign was not tested for on admission.

Laboratory data included a hemoglobin of 12.8 gm. per 100 ml., and a white cell count of 7,300 per cu. mm. with 11 per cent eosinophils. Urinalysis showed a specific gravity of 1.008, no albumin or sugar, 2 to 3 white cells in the sediment, and a positive test for bile. The stool was yellow, semiformal and guaiac-negative. Staining with Sudan III revealed no free fat. Blood chemistries included a fasting blood sugar of 110 mg. per 100 ml., blood urea nitrogen 14 mg. per 100 ml., cephalin flocculation test negative, thymol turbidity 1.0 Maclagan unit, icterus index 102, direct bilirubin 9.6 mg., indirect bilirubin 6.4 mg., cholesterol 647 mg., cholesterol esters 110 mg. per 100 ml., alkaline phosphatase 31.5 Bodansky units, albumin 4.0 gm., and globulin 3.4 gm. per 100 ml. (Fig. 1.)

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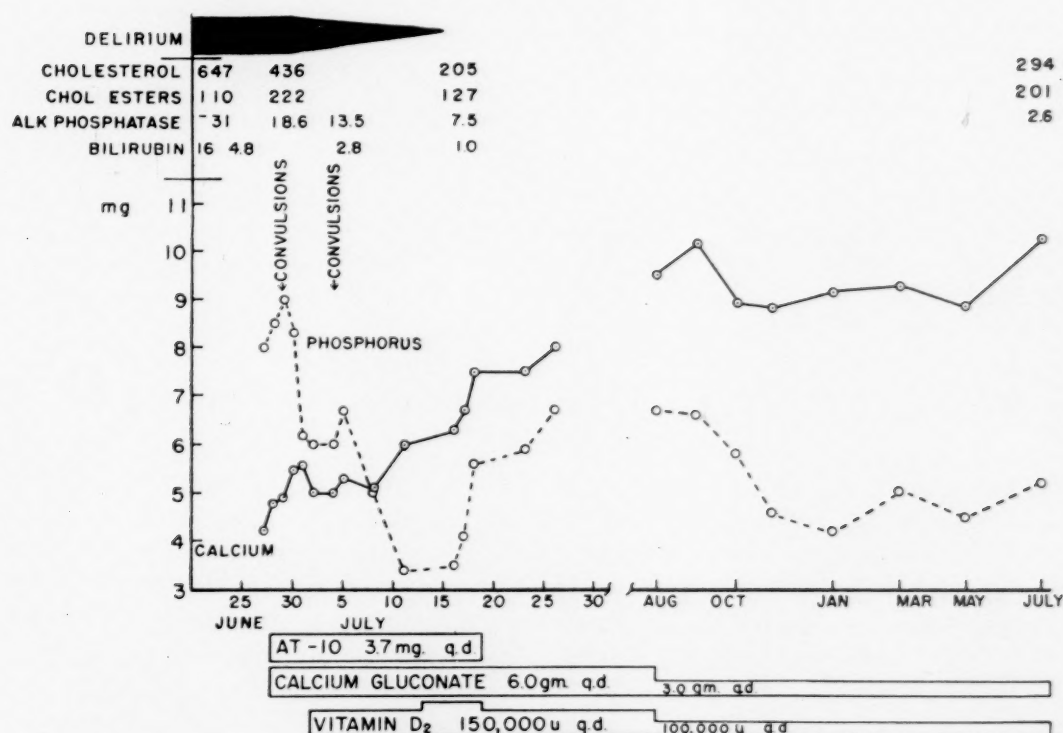


FIG. 1. Chart of blood chemical data and treatment. Alkaline phosphatase values listed in Bodansky units, and other blood chemical values as mg. per 100 ml.

The initial impression was one of chlorpromazine jaundice, depression, and a toxic delirium.

During the first few days of hospitalization the patient was increasingly delirious and disoriented, with agitated and inappropriate behavior. She appeared anxious and at times her speech seemed dissociated. A moderate rigidity of the extremities and trunk was noted. Further laboratory work revealed a prolonged QTc of 0.64 in the electrocardiogram which was otherwise normal, a serum calcium of 4.2 mg. per 100 ml., and phosphorus of 8.0 mg. per 100 ml. The electroencephalogram taken on the sixth hospital day (calcium 4.3 mg.) showed a basic frequency of 8 per second with diffuse moderate slow activity of 5 to 6 per second and paroxysmally slow activity of 4 to 6 per second in all leads. Hyperventilation had no effect. These findings were consistent with delirium or a convulsive disorder. (Fig. 2.) The Chvostek sign was noted to be positive.

A presumptive diagnosis of idiopathic hypoparathyroidism was made on the eighth hospital day (June 28) at which time oral administration of calcium gluconate 2.0 gm. three times a day and dihydro-tachysterol (AT-10) 1.25 mg. three times a day was started. The subsequent course has been outlined in Figure 1. Of note is the persistent hypocalcemia throughout the first nine days of therapy, although the serum phosphorus declined progressively to near normal concentrations during this period. She showed gradual clearing of her delirium manifested by an

increased alertness and more appropriate behavior. She was able to report an episode of fainting two years previously and had also noted that her hands tended to "tighten and draw up" while crocheting several months before admission.

She experienced two generalized convulsions on the ninth hospital day and another three days later. Each was followed by stupor, but was not accompanied by aura, incontinence or postconvulsive coma. A repeat electroencephalogram taken four days after therapy was started showed marked progression of the previous abnormalities (Fig. 2), despite the clinical improvement apparent at that time.

On the tenth hospital day (July 2) vitamin D<sub>2</sub> 50,000 units, and amphotel® 30 ml., each three times a day orally, were added to the regimen. As noted in Figure 1, the serum calcium thereafter rose progressively. There was continuing improvement in her sensorial state with normal alertness, orientation, and ability to relate to the hospital personnel. The elevated serum bilirubin, alkaline phosphatase and cholesterol reverted to normal during the first three weeks of hospitalization. The eosinophilia disappeared, and diarrhea, which was noted shortly after admission, subsided.

Various diagnostic studies were performed after the patient had become essentially asymptomatic. Studies of renal function were normal. X-rays revealed no abnormal bone density, metacarpal shortening or metastatic calcification. The electrocardiogram re-



FIG. 2. Representative tracing of serial electroencephalograms. A, June 27, 1956, before treatment. Serum calcium 4.3 mg. per 100 ml., markedly abnormal, consistent with delirium or convulsive disorder. B, July 2, 1956, after four days of dihydrotachysterol and three days after a convulsion. Serum calcium 5.0 mg. per 100 ml., sharp progression of abnormalities with almost continuous 5 to 6 per second generalized high voltage activity. C, March 12, 1957, after nine months of treatment. Serum calcium 9.2 mg. per 100 ml., very marked improvement but still abnormal with scattered and paroxysmal slowing, consistent with clearing delirium.

verted to normal. An Ellsworth-Howard test was performed July 11 at which time the serum phosphorus was 3.4 mg. per 100 ml. The control urinary phosphorus excretion did not exceed 1 mg. per hour, and

TABLE I  
DETERMINATION OF SERUM CALCIUM AND PHOSPHORUS

Time	Serum Calcium (mg. per 100 ml.)	Serum Phosphorus (mg. per 100 ml.)
0 (start infusion) . . . . .	9.5	6.7
2 hours . . . . .	10.1	6.9
4 hours (end infusion) . . . . .	11.8	7.2
8 hours . . . . .	11.3	7.2
24 hours . . . . .	10.8	5.6

no increase in phosphaturia occurred after the administration of 100 units of parathormone intravenously. Simultaneous testing in a normal control subject was not performed. On July 27, after one week of a standard low phosphorus diet, an intravenous calcium tolerance test was performed. Calcium, 1.28 gm., as the gluconate salt was administered over a

four-hour period, and the serum calcium and phosphorus determinations which were obtained are seen in Table I.

Table II shows the calcium and phosphorus contents noted after twenty-four hour urine specimens were

TABLE II  
CALCIUM AND PHOSPHORUS CONTENTS

Day	24-Hour Urine Calcium (mg.)	24-Hour Urine Phosphorus (mg.)
Control . . . . .	80	288
Test . . . . .	515	434
Test day +1 . . . . .	182	404
Test day +2 . . . . .	171	116

taken on the day prior to the test, the test day, and the subsequent two days.

Following discharge on August 1, 1956, the patient has been followed up in the outpatient clinic and has been maintained on vitamin D<sub>2</sub> 50,000 units twice daily, calcium gluconate 1.0 gm. three times a day, and a low phosphorus diet. She has remained well and has resumed her normal activities. The blood urea nitrogen, serum calcium and phosphorus have remained normal except for occasional slight hyperphosphatemia. (Fig. 1.) In March, 1957 the electroencephalogram showed marked improvement with only rare runs of slow 6 to 7 per second activity. A fairly regular low voltage alpha pattern of 8 to 9 per second was present. The tracing was interpreted as consistent with clearing delirium. (Fig. 2.)

#### COMMENTS

The findings in the present case satisfy the clinical and laboratory criteria for the diagnosis of hypoparathyroidism [1-3]. The tetany, convulsions and mental changes accompanied by hypocalcemia and hyperphosphatemia, in the absence of renal insufficiency or osteomalacia from calcium depletion, are characteristic of this condition. In this patient tetany probably dated back two years before admission but she was able to give this information only after beginning treatment. The hypocalcemia might have been explained on the basis of malabsorption secondary to the chlorpromazine jaundice but the brief duration of the jaundice militates against this possibility. Furthermore, the concomitant hyperphosphatemia could be explained only on the basis of hypoparathyroidism. Further support for the diagnosis is provided by the patient's response to the intravenous administration of

calcium. The increased urinary phosphorus excretion on the test day and subsequent twenty-four hours, when the serum calcium concentration was significantly elevated above the control level, is in direct contrast to the response expected in normal persons [4]. The increased phosphaturia with little change in the serum phosphorus concentration fits the pattern described by Howard and his co-workers [4] in patients with hypoparathyroidism.

In addition the present patient had a complicating illness which, in view of the clinical course and laboratory data, was typical of chlorpromazine jaundice [9]. The elevated serum alkaline phosphatase concentration can readily be explained on this basis, since it returned to normal as the icterus subsided.

The failure of parathormone administration to induce phosphaturia in our patient suggests the diagnosis of pseudohypoparathyroidism [1,2]. Interpretation of this test is hindered because simultaneous testing in a normal patient was not performed and because the serum phosphorus was normal during the test period. Dent [5] has observed a frequent failure of the currently available commercial parathormone preparation to increase urinary phosphorus excretion and believes that in the parathormone test, the serum phosphorus falls only when initially high. Furthermore, evidence has been presented that parathyroid extracts can be separated into more than one active fraction [6], and that the concentration of the phosphaturic moiety is markedly diminished during chemical purification [7]. The usefulness of the Ellsworth-Howard test [8] in the differentiation of hypoparathyroidism from pseudohypoparathyroidism is therefore open to question. Clinically, the lack of metacarpal shortening or metastatic calcification militates against the possibility of pseudohypoparathyroidism [1,2] and suggests that the true diagnosis in the present patient is idiopathic hypoparathyroidism.

Psychosis is unusual as a presenting or predominant symptom in idiopathic hypoparathyroidism [3], and may be an extremely difficult diagnostic problem in the absence of characteristic signs such as tetany. This is well illustrated in the present patient, in whom the psychological disturbance was initially attributed to a psychotic depression or a toxic delirium, and in whom the syncopal episode prior to admission remained unexplained. The true diagnosis was first suggested by electro-

cardiographic changes consistent with hypocalcemia [10] and was subsequently confirmed by the appearance of overt tetany and convulsions, and by other laboratory studies.

The psychological manifestations of this disorder may range from deterioration of intellectual function to frank psychosis with anxiety, irritability, hallucinations, depression and delirium [11-17]. The precise etiology of these symptoms remains unexplained at present, although a close relationship between the mental symptoms and the serum calcium level is apparent during the course of treatment of such patients [11-17]. This is also illustrated by Bartter's [18] observations on patients who undergo successful removal of active parathyroid adenomas. They may manifest psychotic behavior during the acute postoperative period, but respond readily to restoration of a normal concentration of calcium in the serum. However, the absence of frequent psychoses in patients who are hypocalcemic as a result of vitamin D deficiency or malabsorption syndromes suggests that there is not a simple relationship between mental changes and serum calcium levels. Bartter [18] has suggested that the supersaturation of the extracellular fluid which results from the concomitant hyperphosphatemia, in association with the hypocalcemia, may be responsible for certain of the central nervous system manifestations in this disease.

The convulsions described in idiopathic hypoparathyroidism also seem closely related to hypocalcemia, for restoration of the calcium level generally abolishes them [3,15,16]. However, the mechanisms involved and the relationship to classic epilepsy remain debatable points. It may be difficult to differentiate the convulsions of hypoparathyroidism from classic grand mal but in the majority of patients aura, incontinence and postconvulsion coma do not occur [18].

The most distinctive feature in the electroencephalogram is the presence of slow waves, 2 to 5 per second, appearing singly or in series [19]. Abnormalities may be accentuated with hyperventilation, when convulsions are present, or when hypocalcemia is severe [19]. With treatment the abnormalities tend to disappear but the electroencephalogram rarely becomes normal [3,12,16-19]. An interesting feature in the present case, although generally paralleling descriptions of others, was the sharp progression of abnormalities occurring despite institution of therapy and noticeable clinical improvement.

However, the electroencephalogram showing this progression was taken three days following convulsions and may represent changes seen in the postconvulsive period. It may not necessarily be indicative of true epilepsy [20].

The usefulness of dihydrotachysterol and vitamin D in the treatment of hypoparathyroidism is well established [2,21,22]. Although the studies of Albright and his co-workers [22] indicate that dihydrotachysterol produces a more rapid therapeutic response, recent investigations suggest that an equally beneficial effect results from the administration of sufficiently high doses of vitamin D [23]. The response to treatment may be delayed, as illustrated in the present patient in whom a significant increase in serum calcium did not occur until the twelfth day of treatment and the return of a normal serum concentration required over a month. Clinical improvement antedating correction of the hypocalcemia has been suggested in several reports [3,11,17] and is well documented in our patient. It is of interest, however, that her improvement did coincide with a decreasing serum phosphorus concentration, thus further suggesting that the presence of hyperphosphatemia, together with the hypocalcemia, may be of importance in the production of neurological manifestations in this disease. Although Albright and co-workers [22] noted in their studies definite blood chemical improvement after three days of therapy with dihydrotachysterol, the majority of patients with previously untreated chronic hypoparathyroidism in the literature showed a much slower response to treatment. Of possible significance in the delayed response to therapy are the duration of parathyroid insufficiency and the presence of a complicating disease, in this case chlorpromazine jaundice. An increased dose requirement for dihydrotachysterol or vitamin D has been noted during periods of acute stress [12]. By impairing absorption of vitamin D, the intrahepatic biliary obstruction may have initially aggravated the parathyroid insufficiency and may have subsequently played a role in the delayed response to therapy.

#### SUMMARY

A case of idiopathic hypoparathyroidism presenting as a psychosis and complicated by chlorpromazine jaundice is described. The difficulty in establishing the proper diagnosis in this condition when psychosis is the predominant

manifestation is emphasized. Psychological abnormalities and other central nervous system signs associated with hypoparathyroidism are discussed. In the present case symptomatic improvement followed the institution of therapy despite the persistence of hypocalcemia. Initially the clinical course was better correlated with the correction of the hyperphosphatemia. It is suggested that there may be a closer relationship of the central nervous system manifestations of hypoparathyroidism to hyperphosphatemia than has previously been appreciated.

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# Haemodialysis in Acute Acetylsalicylic Acid Poisoning\*

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ACETYLSALICYLIC acid (aspirin) is relatively non-poisonous but nevertheless it is not infrequently employed as a suicidal agent. In the United States, for example, salicylic acid compounds are responsible for approximately 4 per cent of all fatal cases of poisoning caused by ingestion of solids and liquids [9]. After absorption, acetylsalicylic acid hydrolyzes rapidly in the organism, and thus presents the same clinical picture as salicylic acid poisoning. In adults, death has been caused by 10 to 30 gm. sodium salicylate or acetylsalicylic acid, but much larger quantities have been consumed (in one case 130 gm. aspirin) without death [6].

In recent years, haemodialysis by means of the "artificial kidney" has been tried as a treatment in cases of severe poisoning. Doolan et al. [4] in 1951 dialysed an adult male who had a blood concentration of 55 mg. salicylic acid per 100 ml. It was estimated that 1.3 gm. salicylic acid was removed by the dialysis, which had to be interrupted after one hour for technical reasons, but the patient died some hours later as a result of the poisoning. Schreiner et al. [9] in 1955 submitted the first known instance of the successful use of haemodialysis in a case of salicylate poisoning. The patient was a forty year old man who had consumed approximately 210 gm. aspirin. He was comatose on admission to hospital. The blood concentration of salicylate was 91 mg. per 100 ml. It was possible to remove 9.4 gm. salicylate by haemodialysis, during which the blood concentration fell to 34 mg. per 100 ml. The patient was completely well on the day following the dialysis. Later, another haemodialysis was carried out on a woman who had consumed 166 gm. aspirin. In this case the blood concentration of salicylate fell from 115 to 29 mg. per 100 ml. The patient was revived but died five days later from a violent gastrointestinal hemorrhage. Leonards [8] in 1955

dialysed two patients with salicylate poisoning, with excellent results. Details are given for one patient only: he had taken a large dose of methyl salicylate, and on admission to the hospital had a blood concentration of 130 mg. per 100 ml. salicylate. It was possible to remove 9.5 mg. salicylate by haemodialysis, the salicylate concentration falling to 30 to 40 mg. per 100 ml. The patient recovered from coma, and the respiration rate fell very quickly.

## CASE REPORT

A forty-one year old man consumed, with suicidal intent, 150 gm. acetylsalicylic acid dissolved in a fruit drink. The patient was admitted to the emergency ward for cases of poisoning, Bispebjerg Hospital, Copenhagen, and treated with sodium bicarbonate and carbogen. Because of shock he was also given dextran® and a blood transfusion. Renal insufficiency developed immediately and he was transferred next day to the dialysis department of the Municipal Hospital, Copenhagen. On arrival here the patient showed the classic signs and symptoms of acute salicylic acid poisoning. The effects on the central nervous system were manifested as pronounced hyperpnoea and polypnoea, as well as hyperpyrexia. The patient was somnolent and confused, with restlessness and twitching in the extremities. He had previously complained of tinnitus and reduced hearing. The gastrointestinal symptoms were violent, with vomiting (which the patient had experienced before admission), thirst, diarrhoea, violent gastralgias and distended abdomen. There was also tachycardia and intense cyanosis. As a consequence of the central respiration-stimulating effect of the salicylic acid, alkalosis was found, but with a low carbon dioxide tension (pH in arterial blood 7.55, pCO<sub>2</sub> 21 mm.). The electrocardiogram showed a slightly prolonged QT interval. The patient had already received vitamin K at Bispebjerg Hospital because of the tendency to haemorrhagic diathesis, but the prothrombin concentration was nevertheless reduced to 58 per cent. As a result of the toxic effect of the salicylic acid on the liver, a pronounced rise in the serum

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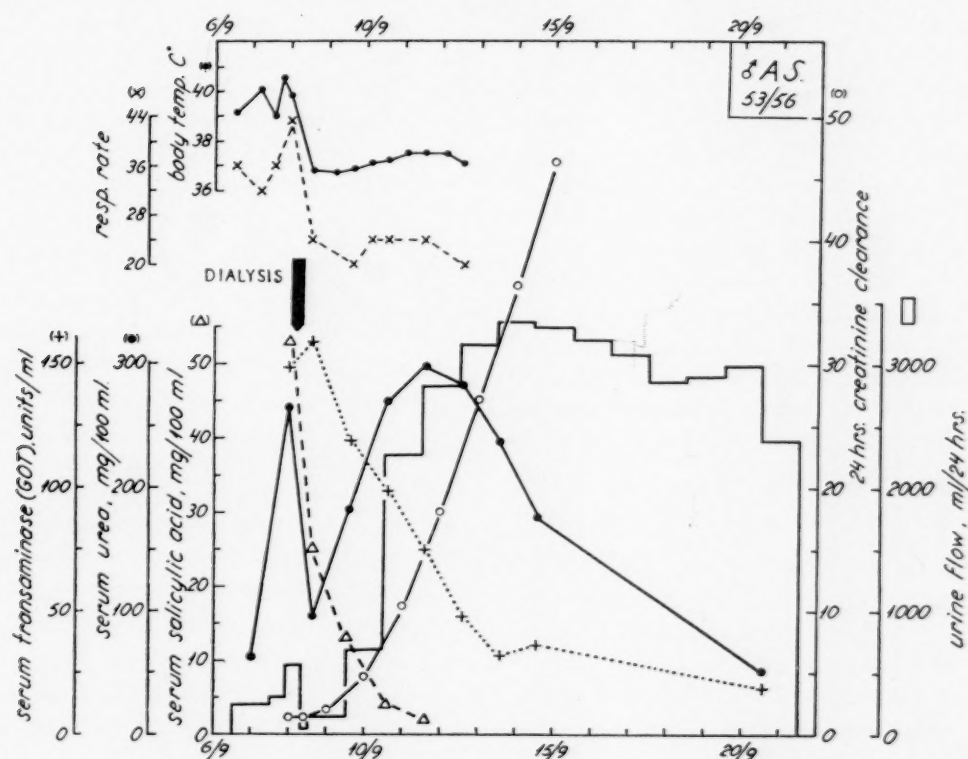


FIG. 1. Effect of dialysis on serum salicylic acid  $\Delta$  and urea . . . concentrations, temperature and respiration. Renal function improved rapidly after the haemodialysis, and the remaining salicylic acid was eliminated spontaneously during the following days. The salicylic acid poisoning caused a marked increase in the serum transaminases (normal value 10 to 40 units/ml.).

transaminases was found. Apart from marked sweating, no skin symptoms were found.

Shortly after admission the patient showed increasing stupor and a seriously aggravated general condition, incipient cardiovascular collapse and more superficial respiration. As the amount of acetylsalicylic acid consumed could well be fatal, and elimination had practically ceased because of renal insufficiency, immediate haemodialysis was indicated.

The dialysis was carried out forty-eight hours after the patient consumed the aspirin, by means of the Skeggs-Leonards dialyser. The technic and bath fluids did not differ from those used in cases of acute renal failure [2]. The blood flow in the apparatus was 600 ml./minute, the urea clearance 180 ml./minute. The patient was dialysed for five and a half hours and no complications were observed.

The effect of the dialysis was dramatic: the respiration rate fell from 44 to 24 per minute, the temperature from 39.8 to 36.8°C. The sensorium cleared, the restlessness disappeared and the cyanosis decreased. The serum salicylic acid (determined by Faber and Schmidt's method [5]) fell from 51.0 to 24.8 mg. per 100 ml. (The patient weighed 72.3 kg. The amount of salicylic acid removed by the dialysis could not be determined.) The serum urea fell from 264 to 64 mg. per 100 ml. (Fig. 1.)

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The day after the dialysis, the patient was completely conscious. The respiration rate was 20 to 24. The temperature was normal, and the circulation now completely stable.

During the next few days renal function improved rapidly. On the fourth day approximately 5 gm. salicylic acid was excreted in the urine, and the serum salicylic acid concentration fell to values which could not be measured. The patient's course was quite uncomplicated, and on discharge the patient was completely well somatically.

#### COMMENTS

The lethal dose of acetylsalicylic acid is not known, but presumably amounts over 10 gm. can produce severe poisoning in adults. Fatalities in children have been observed with a few grams [7].

Salicylate is mainly excreted through the kidneys, as approximately 80 per cent of the amount consumed can be recovered in the urine. The compound is excreted by means of a "four-component system," being filtered, reabsorbed and secreted in the form of free salicylate, and also in the form of con-

jugated compounds. Tubular reabsorption is promoted in acid urine, excretion is increased in alkaline urine [3]. The rate of elimination can therefore be increased to some extent by supplying bicarbonate, but under some circumstances this therapy is inadequate. If the poisoning is severe and of long duration, irreparable brain damage may ensue. Not infrequently, renal function may be severely affected, with anuria. Under such circumstances, rapid termination of the poisoning becomes essential. As a specific antidote is unknown, the question of possible treatment by means of haemodialysis becomes of immediate importance.

It is undoubtedly a fact that 50 to 80 per cent of the salicylate in human plasma is bound to the plasma proteins [6], but the binding apparently is so loose that the compound can be removed from the blood by dialysis [7]. In the cases referred to, in which haemodialysis was used as treatment in salicylate poisoning, only a fraction of the amount consumed was actually removed during the dialysis (at most 10 gm.), but the beneficial clinical effect of the dialysis indicates that this small amount is, nevertheless, enough to lower the salicylate concentration in the blood to non-toxic values. The discrepancy is no doubt due to the fact that the greater part of the ingested salicylate usually escapes absorption from the gastrointestinal tract as a result of vomiting and diarrhoea. This is also supported by the fact that such small amounts as 10 to 30 gm. may cause death.

Schreiner [9] has compared the clinical course in a haemodialyzed and a conservatively treated patient. The dialysis was presumably life-saving, and in any case the duration of illness was considerably reduced, decreasing the risk of brain and lung complications.

In the case of the patient under discussion, there was no doubt that the dialysis resulted in an abrupt termination of the symptoms of poisoning, and presumably saved his life, as there was indication of commencing circulatory collapse. For technical reasons the amount removed was not determined: if the volume of distribution for the salicylic acid is taken as equal to the extracellular volume, probably about 5 gm. of salicylic acid was removed.

From what has been stated, the indications for haemodialysis of salicylate poisoning are as follows: all severe cases of poisoning, especially if

(1) the elimination of salicylate is slow as a result of acute or chronic renal insufficiency, or (2) coma or signs of respiratory and circulatory depression are present. In any event such cases should be transferred to a haemodialysis department.

#### SUMMARY AND CONCLUSION

A forty-one year old man consumed 150 gm. of acetylsalicylic acid with suicidal intent. The classic signs and symptoms of salicylic poisoning developed, with superimposed renal insufficiency. On haemodialysis, which presumably saved his life, the serum salicylic acid concentration was reduced from 51.0 to 24.8 mg. per 100 ml. The renal function rapidly returned to normal. Early treatment of cases of severe poisoning by means of haemodialysis is strongly recommended.

*Acknowledgment:* Our thanks are due to Miss Inger Gad, PH.D., for carrying out the salicylic acid determinations.

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# Xanthoma Tuberosum\*

## A Six-Month Control Study

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THE opportunity to study a young man with xanthoma tuberosum, in a controlled environment for a six-month period, was recently made available at the U. S. Federal Penitentiary Hospital, Lewisburg, Pennsylvania. Throughout the entire study period the patient was hospitalized, and under constant observation. Laboratory studies were made available at this institution; Geisinger Memorial Hospital, Danville, Pennsylvania; the National Heart Institute, Washington, D. C.; and the Donner Laboratory of the University of California, Berkeley, California.

### CASE REPORT

W. M., a twenty-six year old white man, was born in Reidsville, North Carolina. He had the usual childhood illnesses, including varicella, rubeola and mumps. At age seven a urinary infection was noted which persisted for several days. No accurate records are available. After this short period without cardiac or other vascular pathology, he remained asymptomatic, with a normal urine examination in adolescence. The only other childhood illness was intermittent swelling of both knee joints that would last for several days. No other joints were involved. No residual deformity or arthralgia persisted in adolescence. No cardiac murmur or other rheumatic symptomatology had been noted.

The patient's father was in his early fifties, living and well. His mother had died at age thirty-five in childbirth. (Fig. 1.) A blood cholesterol determination of the father in our laboratories revealed a level of 378 mg. per cent. One uncle on the maternal side was known to have died of vascular disease (coronary sclerosis). There was a history of coronary artery disease and a cerebrovascular accident in a paternal grandmother. The paternal grandfather also had angina pectoris. The patient's siblings, two brothers and two sisters, were all living and well. No history of diabetes mellitus or gout was known in the family.

In 1952, while working in a Navy kitchen, the patient was accustomed to taking 1 to 2 pints of ice cream and 1 quart of milk daily. In August of that year a friend called attention to a yellow deposit on the

skin of the right elbow. This had not been noted previously by the patient. There was no associated pruritus. A similar lesion was noted on the other elbow, and both appeared to increase in size within the next few weeks. In September of that year small yellow papules were noted on the back of the neck.

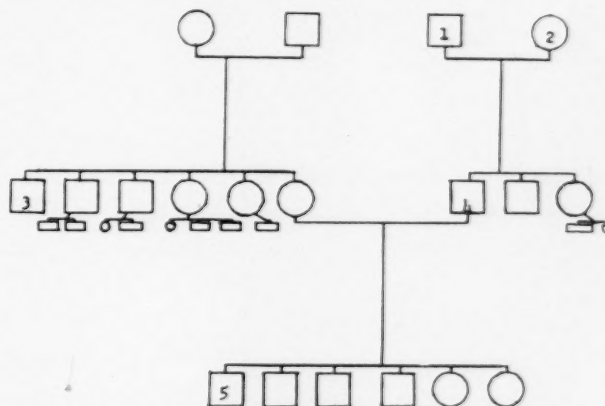


FIG. 1. 1, Paternal grandfather; angina pectoris. 2, Paternal grandmother; coronary sclerosis; died of cerebrovascular accident. 3, Uncle; died of coronary sclerosis. 4, Patient's father; living and well, blood cholesterol, 378 mg. per cent. 5, Patient; xanthoma tuberosum.

These were followed almost immediately by tuberos deposits on both buttocks. In November a single nodule developed on the left knee.

In December, 1952, the patient entered the U. S. Naval Hospital, Portsmouth, Virginia, with a diagnosis of xanthoma tuberosum. Physical examination at that time was essentially negative except for the skin findings. His weight on admission was 143 pounds, and four months later (March, 1953), upon discharge from the hospital, it was 4 pounds less. Over both elbows there were raised plaque-like lesions, about 5 cm. in diameter, which were circular in outline, well circumscribed and filled with yellowish nodules of various size. Similar lesions were present on the back of the neck, except that here there was a tendency to more discrete papules, less erythematous than the lesions on the elbow. Large nodules about 1 to 2 cm. in diameter were present on both buttocks, and a

\* From the U. S. Federal Penitentiary Hospital, Lewisburg, Pennsylvania.

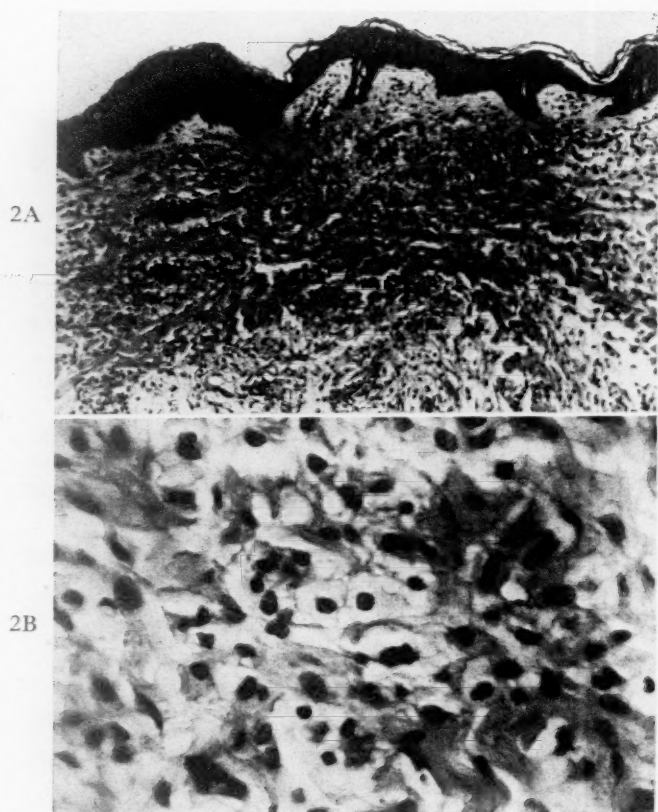


FIG. 2. A, low power view of xanthoma tuberosum. B, high power view of same section revealing xanthomatous (foamy) cells.

smaller deposit was found on the left knee, about 2 mm. in diameter.

Laboratory studies revealed normal urine, blood Kahn test and hematological findings. The sedimentation rate (Wintrobe) was 23 mm. The blood cholesterol on admission was 626 mg. per cent. Blood sugar, urea, bromsulphalein and other liver function studies were all within normal limits.

X-ray examination of the chest was negative for abnormalities, and the electrocardiogram was within normal limits. Ophthalmoscopic examination was negative. Shortly after admission the patient complained of pain in the right knee and a diffuse, slightly painful swelling over the infrapatellar bursa was noted. This subsided within one week without any specific therapy. X-ray examination was negative for abnormalities, and the orthopedic consultant believed that this represented a xanthomatous infiltrate into one of the structures associated with the knee joint.

Skin biopsy was obtained of one of the lesions, a nodule which was yellow in color and elevated 1 to 2 mm. from the adjacent surface. On section the cut surface was orange in color. On microscopic section, the overlying epidermis showed mild diminution in size of the rete pegs. The most striking changes were in the dermis and underlying subcutaneous connective

tissues, scattered through the interstices of which there were myriads of xanthoma cells characterized by small, round or slightly lobulated nuclei and abundant clear cytoplasm, which was frequently reticulated. Occasional cells contained more than one nucleus and nucleoli were prominent. (Fig. .)

The patient was given a low cholesterol diet, and multiple vitamin and yeast tablets by mouth. On this therapy the blood cholesterol receded from 626 mg. per cent to 456 mg. per cent. No definite change in the lesions was detected by the patient. He was discharged March 15, 1953, and was instructed to maintain dietary restriction.

In the three-year period following release from the Naval hospital the patient maintained careful dietary regulation. His weight remained essentially the same. One small nodule developed on the right knee in the course of six months during the latter part of 1955. The remaining xanthomatous lesions elsewhere persisted and appeared somewhat larger in size.

On arrival at the U. S. Federal Penitentiary, Lewisburg, Pennsylvania, on March 30, 1956, he had no cardiovascular complaints. The skin lesions were essentially asymptomatic except for those on the buttocks which caused discomfort upon sitting. The blood pressure was 140/80 mm. Hg and weight, 137 pounds. The general physical examination was within normal limits. The patient presented the following lesions as of that date:

Over the neck there were some twenty pea-sized nodular elevations, waxen, with a raised margin and a yellowish central excrescence. (Fig. 3.)

A large circinate tuberos deposit was seen over the right elbow, approximately 5 by 5 cm. in size, with a satellite nodule of 2 cm. adjacent. The lesion was raised, irregular and roughened. (Fig. 4.) The infiltration on the left elbow was rather soft and cystic, and appeared somewhat reddened, as if recently the site of inflammation. There were numerous small papular lesions adjacent.

Examination of the palms and also the extensor tendons of the digits in the region of the carpal tunnel revealed numerous xanthoma tendinosa and plana. These appeared as an irregular thickening and plaque-like elevations on the tendons. The skin appeared to be non-adherent in some areas.

On the right buttock were three large nodular deposits. The largest measured 3 by 3 by 3 cm., the two smaller approximately 2 cm. each. They were all somewhat softened and reddened. On the left buttock was a rather firm, pedunculated lesion measuring 5 by 5 cm., protruding several centimeters from the adjacent skin, and very tender to pressure. The margins were quite sharply demarcated. (Fig. 5.)

On the left knee the patient had a rather firm nodule over the lateral aspect of the left patella, approximately 2 by 2 cm. in size, and somewhat mobile. The most recent lesion was seen to be just beginning along the right patellar margin. Especially

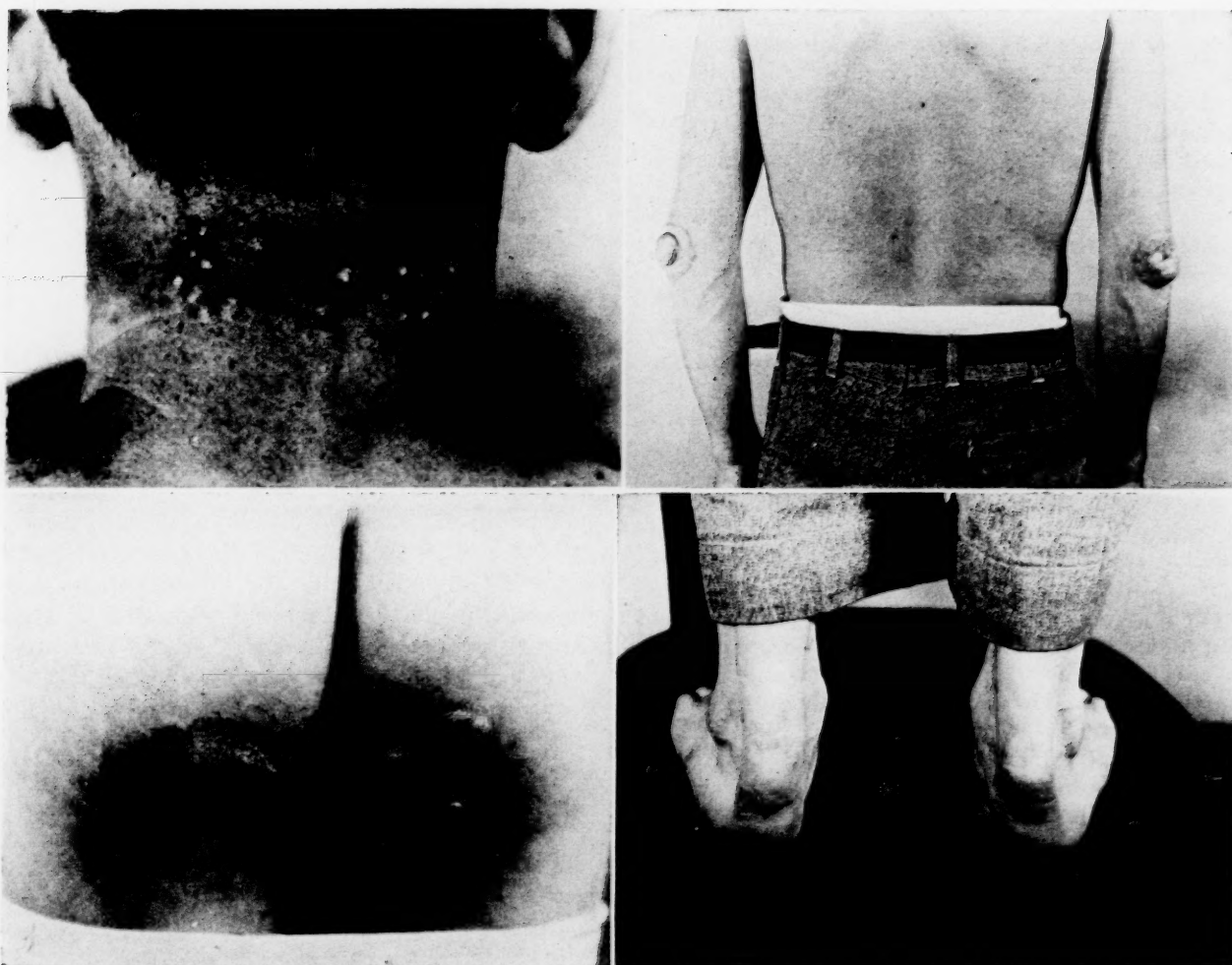


FIG. 3. Photograph of neck showing xanthomatous deposits in skin.

FIG. 4. Tuberos areas around both elbows are demonstrated. Definite color change and softening of these lesions occurred with administration of estrogens.

FIG. 5. Painful tuberos lesions on both buttocks are well demonstrated.

FIG. 6. Xanthoma tuberosum in both gastrocnemius tendons.

prominent in the area were multiple yellowish sand-like deposits in the skin, undoubtedly similar xanthomatous deposits as yet in insufficient abundance to form nodular lesions.

Over the posterior aspect of both Achilles tendons were several xanthoma tendinosa, 3 by 3 cm. in size, which were also somewhat painful and tender to the patient when wearing shoes. (Fig. 6.)

Ophthalmoscopic examination failed to reveal any lipemic deposits or evidence of lipemia retinalis. Examination of the heart and lungs was negative for abnormalities. No liver or spleen enlargement was noted. Peripheral vessels were palpated throughout, with good pulsations. Oscillometric examination was also within normal limits.

Laboratory work-up on admission revealed normal hematologic findings. The sedimentation rate was 14 mm. (Wintrobe). The blood sugar was 93 mg. per

cent fasting, and an oral glucose tolerance test revealed a somewhat prolonged curve, the two-hour specimen being 135 mg. per cent. Other basal laboratory work, including liver function tests, serum amylase and uric acid, were all normal.

X-ray studies including chest, gallbladder and complete gastrointestinal series, and soft tissue views of the extremities for calcification were all normal. The electrocardiogram also was negative.

Repeated urine examinations were performed to rule out nephrosis or chronic nephritis. No edema, hematuria, casts or albuminuria were noted. No evidence of myxedema or hypothyroidism was apparent clinically. The basal metabolic rate was normal. Chronic pancreatitis was unlikely by clinical history, and lack of steatorrhea, pancreatic calcification or weight loss. Biliary cirrhosis was ruled out by the absence of hepatosplenomegaly, icterus or fever.

The plan of study during the six-month period was briefly as follows: The patient was hospitalized during the entire period. After determining the initial lipid and cholesterol levels, he was given a 20 gm. fat diet. Additional protein was supplied by the use of lesofac®\* which was found palatable in fruit juices and other liquids. The diet was maintained throughout the entire study. Satisfactory basal laboratory levels were established after a six-week period (April 5 to May 21, 1956).

On May 22, 1956, administration of estinyl®, 0.5 mg., was begun. This was taken as a single tablet at bedtime. A minimal degree of nausea and gastrointestinal intolerance was subsequently noted, and the only side effect was a loss of libido. Gynecomastia did not occur. The medication was maintained until June 24, 1956.

For the next month (June 25 to July 29) an intravenous injection of 40,000 units of heparin was administered daily. Lee-White coagulation times were performed, and no serious side effects occurred.

On July 30, 1956, administration of cytellin,† two teaspoonfuls before each meal, was begun. This liquid medication was soon taken without discomfort by the patient. The dosage was maintained for the duration of the study, i.e., the last three months.

On August 28, 1956, 2 gr. of desiccated thyroid were administered daily in addition to the 20 gm. fat diet and the sitosterol before meals. The thyroid was given without incident until September 25, 1956.

On September 26, 1956, and continuing through the last month of the study, nicotinic acid, 500 mg. six times daily, was given for a total daily dose of 3 gm.

#### COMMENTS

Xanthoma tuberosum has been considered to be the homozygous state of essential familial hypercholesteremia [1]. This metabolic disorder is characterized by an increased blood cholesterol, the metabolic abnormality being transmitted as a dominant homozygous trait in patients with xanthoma tuberosum, tendinosum and planum, and as simple hypercholesteremia without skin changes in the heterozygous form.

\* Lesofac (Wyeth), low sodium, low fat food. Protein 50 per cent, carbohydrate 39.2 per cent, fat 1.0 per cent including cholesterol 0.025 per cent, ash 5.8 per cent and moisture 4.0 per cent. The sodium content was 0.02 per cent. This product supplies 3.7 calories per gram, or 105 calories per ounce. Ingredients consist of casein and lactalbumin, hydrolyzed rice flour, sucrose, dibasic calcium phosphate, potassium carbonate and magnesium oxide. The vitamin content was B<sub>1</sub> 1.0 mg. per 50 gm., B<sub>2</sub> 2.0 mg. per 50 gm., and niacinamide 10 mg. per 50 gm.

† Cytellin (Lilly), a liquid suspension of plant sterols containing 20 per cent sitosterols; 80 to 90 per cent of the total is beta-sitosterol, and the remainder is largely dihydro-beta-sitosterol, derived from tall oil.

Piper and Orrild [2] have postulated that essential familial hypercholesteremia is transmitted as a dominant trait, the occurrence of xanthoma not being conditioned by homozygous transmission but depending largely upon the level of serum cholesterol.

While the individual family members could not be checked personally, the finding of hypercholesteremia in the patient's father (378 mg. per cent) and the history of vascular disease on the paternal side, together with the finding of coronary disease on the maternal side (one uncle), suggests a homozygous transmission in our case. (Fig. 1.)

The principal clinical manifestations of the inherited form of this disease are: xanthelasma, xanthoma planum, tuberosum and tendinosum, infiltration of the lining of the bile ducts, and endocardial and arterial intimal cholesterol deposits. Corneal arcus often occurs early, with premature coronary artery disease. Coronary atheromas can develop at an early age and are not uncommonly fatal in the homozygous state of essential familial hypercholesteremia [1]. Occlusive vascular disease of the extremities has been noted in a high percentage of this group.

Our patient has not demonstrated clinical evidence of vascular disease after a four-year period of visible xanthoma. This may be explained to some extent by the unusual ultracentrifuge results to be described later.

Xanthoma tuberosa are characterized as nodular elevations of the skin, usually isolated, not confluent, or aggregated in small groups. They have an irregular shape, are yellowish in color, and vary in size. Their favorite locations are the extensor surfaces of the arms, the elbows and buttocks. There is apt to be superficial hyperkeratosis. The nodules are not pruritic.

Oral, mucosal and laryngeal deposits are rarely found, as distinguished from xanthomata multiplex disseminata [3]. Xanthoma diabeticorum is an eruptive form occurring with the lipemia and hypercholesteremia of severe diabetes mellitus, and is characterized by itchy, papulopustular eruptions which are evanescent, reappearing with the more severe metabolic state.

Wijnhausen [4] has described a case in which xanthomatous lesions were noted thirty-four days prior to the appearance of sugar in the urine. Attacks of ileus, bowel obstruction and fever were present, and one year later chronic pancreatitis was found on exploratory laparot-



TABLE II  
ANALYSIS OF SERUM LIPIDS\*

Date	Total Cholesterol (mg. %)	Cholesterol/Esters (% of total)	Total Phospholipids (mg. %)	Total Triglycerides (mg. %)
April 8, 1956.....	<i>150-240</i> 570	<i>70-75</i> 75	<i>150-250</i> 344	<i>100</i> 269 (clear fasting serum)
3 hr. p. c.....	638	72	340	380
June 18, 1956.....	446	71	378	234
July 24, 1956.....	624	75	414	185
August 27, 1956.....	466	73	351	71
September 27, 1956.....	412	74	335	174

NOTE: Italicized figures stand for normal values.

\* Performed by Dr. Donald S. Fredrickson, Heart Institute, National Institutes of Health, Bethesda, Maryland.

one month's therapy with cytellin, 8 cc. before each meal, alpha-2, beta and gamma globulin were diminished. The pattern in Figure 10 was obtained after the addition of 2 gr. of thyroid daily to the same cytellin dosage (September 25, 1956). A distinct drop in albumin occurred, together with some elevation of the alpha-2 and beta globulin fractions. After the addition of 3 gm. of nicotinic acid daily to the cytellin dosage there was an equivocal decline in all globulin fractions.

Ultracentrifuge studies were performed by the Donner Laboratory of the University of California. The results are shown in Table III. Gofman [6] has pointed out that this pattern is a mixed one, but primarily that of xanthoma tendinosum rather than of xanthoma tuberosum. The major elevation was in the standard Sf 0-12 and 12-20 range. While the standard Sf 20-100 and 100-400 values were elevated, they were

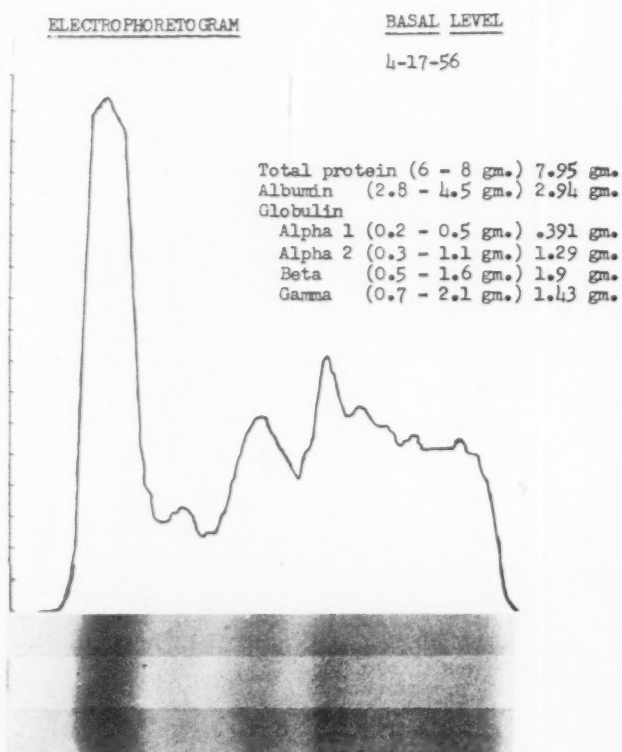


FIG. 7. Basal level electrophoretogram.

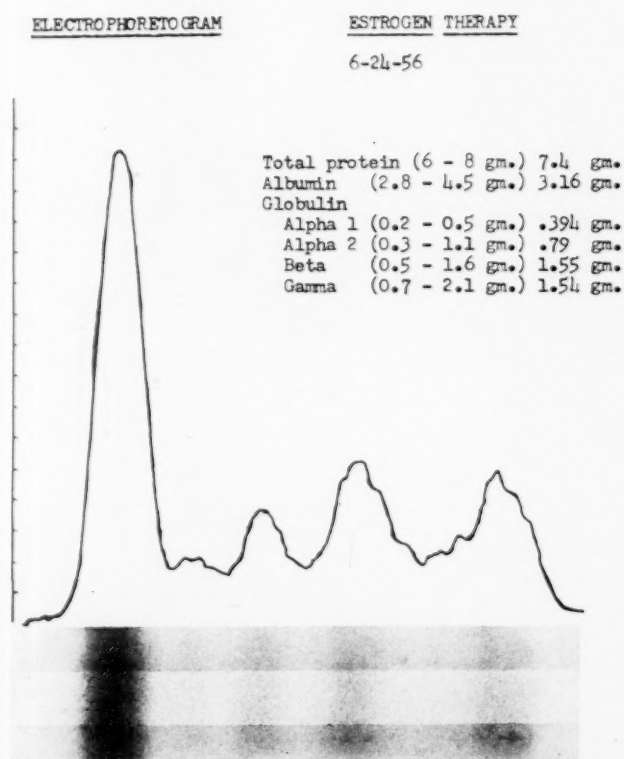


FIG. 8. Electrophoretogram after one-month course of estinyl, 0.5 gm. every day.

TABLE III  
SERUM LIPOPROTEIN CONCENTRATIONS (MG. %) IN XANTHOMA TUBEROSUM  
ULTRACENTRIFUGE STUDY, USING STANDARD TECHNICS\*

Case	Sf 0-12	Sf 12-20	Sf 20-100	Sf 100-400	"Atherogenic Index"
Normals (mean).....	336	65	92	56	.....
Xanthoma tuberosum (mean).....	206	128	616	650	.....
Xanthoma tendinosum (mean).....	793	150	128	36	.....
Patient.....	964	213	229	119	195 units

\* Performed by Dr. John W. Gofman, Donner Laboratory, University of California, Berkeley, California.

much lower than are usually observed in classic cases of xanthoma tuberosum.

Gofman [7] has pointed out that, in contrast to patients with xanthoma tendinosum, none of his series of patients with xanthoma tuberosum reported the presence of lesions in childhood. He found that in males xanthoma tuberosum develops at a much younger age than in females. Familial lipoprotein patterns on ultracentrifuge analysis often tended to show inheritance of the trait disorder, often more consistently than hypercholesteremia.

*Results of Therapy.* Diet: Urbach [8], in his series, found that dietary cholesterol restriction alone had no effect in familial xanthomatosis. Restriction of dietary cholesterol and animal fat elicited an occasional response, especially if the vegetable fat intake was increased. He found restriction of total daily fat intake under 25 gm. to be effective. A decrease in serum total cholesterol and esters, total (turbidimetric) lipids and phospholipids occurred. The response was greatest in those without tendon lesions. The

#### ELECTROPHORETOGRAM

#### HEPARIN THERAPY 7-23-56

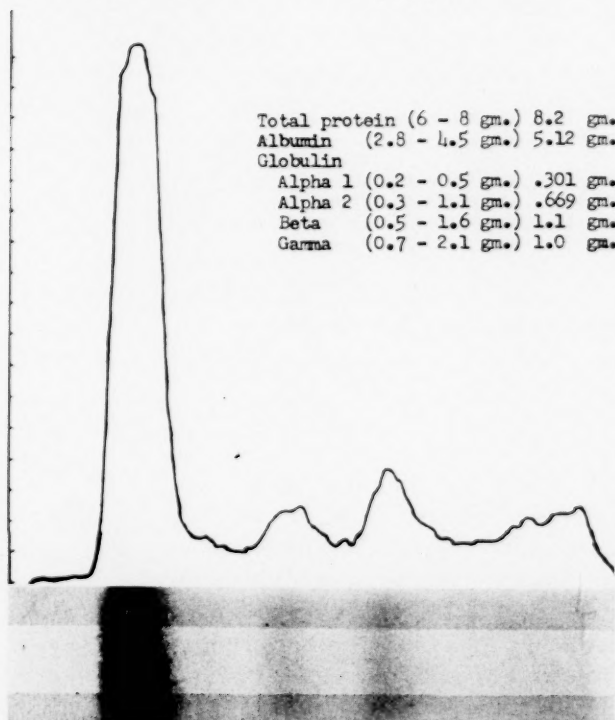


FIG. 9. Electrophoretogram after one month of intravenous heparin, 40,000 units every day.

SEPTEMBER, 1958

#### ELECTROPHORETOGRAM

#### CYTELLIN PLUS THYROID THERAPY 9-25-56

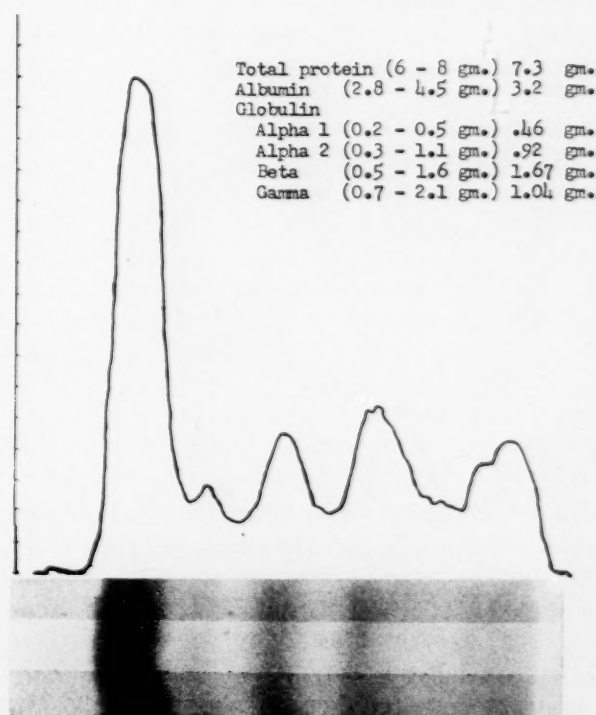


FIG. 10. Electrophoretogram after cytellingin and 2 gr. of thyroid daily.

serum lipids became normal after two to four months. If the fat intake was then increased at this point, skin lesions did not recur. Over a period of seven to fourteen months no effect on extensive skin or tendon lesions was noted, and the serum lipid levels remained elevated. Occasionally angina pectoris disappeared, and the ballistocardiogram showed improvement.

There is a limit beyond which dietary restriction will not readily lower the cholesterol level [9]. In nearly absolute starvation the serum cholesterol rises, but if 40 to 50 gm. of carbohydrate are consumed daily, just enough to prevent ketosis, the serum cholesterol falls. Simultaneous reduction of the Sf 12-20 fraction on ultracentrifuge analysis has been noted on a low fat diet.

The results of a low fat (20 gm.) diet are demonstrated in our patient. The serum cholesterol of 626 mg. per cent present at the onset of clinically apparent xanthomatosis (December, 1952) was reduced to 456 mg. per cent, after a four-month period at the Portsmouth Naval Hospital.

During the next four years the patient maintained some dietary restriction voluntarily. Despite this, the serum cholesterol on admission to study on April 5, 1956, was 633 mg. per cent. With more stringent dietary regulation this receded to 558 mg. per cent. A less definite response was obtained at our institution possibly because of the dietary restriction previously in effect.

*Estrogen therapy:* A depression of the plasma C/P (cholesterol/phospholipid) ratio toward normal occurs with estrogen-induced hyperphospholipemia [10]. The serum cholesterol level may or may not fall.

Oliver [11] found that administration of 0.2 to 0.6 mg. of ethinyl estradiol daily for at least eleven weeks elicited a substantial fall in serum total cholesterol, especially of the ester fraction. He found the serum phospholipids to be unchanged. Side effects included gynecomastia, nausea, dizziness, listlessness, fatigue, depression and feminization. The same author [12] found that there was no difference in results with ethinyl estradiol in 200  $\mu$ g. or 1 mg. dosage. The per cent fall in total C/P ratio was greater than the decline in total cholesterol.

Several effects were noted from the 0.5 mg. dosage of estinyl given our patient daily for one month. All of the skin lesions became softer, and those of the buttock presented definite

evidence of cholesterol absorption. In addition, vascularization and hyperemia became evident, with a peculiar pinkish tinge to the deposits. This effect persisted only for a short time after the estrogen was discontinued, and was not seen with any of the other agents.

The serum cholesterol receded from a level of 558 mg. per cent to 456 mg. per cent. (Table I.) A corresponding drop in the beta globulin fraction also occurred. (Fig. 8.) Lipid fractionation analysis demonstrated an elevation of the phospholipids and a decrease in total neutral fat and cholesterol. The ester ratio, however, was not materially affected. (Table II.)

*Heparin therapy:* An increased C/P ratio frequently has been noted in patients with xanthoma tuberosum, and there is often twice as much cholesterol combined with beta as with alpha lipoprotein. A dosage of 40,000 units of heparin, given intravenously daily for one month, failed to show any lowering of serum cholesterol in our patient. (Table I.) Instead the level rose from 456 mg. per cent to 624 mg. per cent. (The lower level represented the effect of the previous estinyl.) The electrophoretogram (Fig. 9), however, revealed further lowering of the beta and gamma globulin fraction, and some rise in the albumin. Lipid studies revealed a decrease in neutral fat and a rise in total phospholipids. (Table II.)

*Plant sitosterol therapy:* Our patient took cytellin in 8 cc. doses before each meal. A reduction in serum cholesterol from 624 mg. per cent to 486 mg. per cent occurred within the first month. Electrophoretic study revealed decreased alpha-2, beta and gamma globulin fractions. Partition of the serum lipids revealed diminished phospholipid and neutral fat.

*Thyroid therapy:* Effective results in xanthoma tuberosum have been obtained using 2 gr. doses of thyroid in subjects without evidence of coronary artery disease [13].

The exact mode of action of thyroid in lowering the serum cholesterol is speculative. Jones [14] states that the effect of thyroid is concerned with the distribution of cholesterol between plasma and tissues, rather than an action on total body synthesis or utilization. Rosenman [15] has shown that hyperthyroidism is associated with an increased rate of hepatic synthesis, destruction and intestinal excretion of cholesterol. Thyroxine can neutralize the effect of estradiol on serum cholesterol, if appropriate doses are given [16].

Our patient received 2 gr. of thyroid daily. The serum cholesterol remained essentially unchanged. Electrophoretic study revealed a decreased albumin and increased alpha-1, alpha-2 and beta globulin fractions. Lipid study revealed decreased serum phospholipids and some increase in neutral fat.

*Nicotinic acid therapy:* Parsons [17] and his group have recently reported on results with 0.5 gm. of nicotinic acid given six times daily for from four to twelve weeks. (The amide, which gives fewer side effects, was found ineffective.) Administration of nicotinic acid in their series produced a decrease in the serum cholesterol and a reduction in the beta lipoprotein fraction. The concentration of total lipids in the plasma was reduced in most of the patients, but to a lesser degree than was the concentration of cholesterol.

In the patient herein described a definite decrease in serum total cholesterol occurred in the initial period of dosage. Unfortunately the side effects were so severe that our patient was unable to continue the full dosage. While the vasodilatory effects were eventually tolerated, marked nausea and intestinal hyperperistalsis developed. This was finally controlled by the administration of pro-banthine® before each dosage.

#### SUMMARY

1. A patient with familial hypercholesteremia and xanthoma tuberosum was studied for six months in a controlled prison environment.

2. The use of a 20 gm. fat diet alone for a six-week period produced a significant fall in serum cholesterol (626 to 456 mg. per cent) in 1952 and later from 633 to 558 mg. per cent when the patient was rehospitalized in 1956.

3. The use of 0.5 mg. ethinyl estradiol produced definite softening and vascularization of several tuberous deposits, lowering of the serum cholesterol from 558 to 456 mg. per cent, and a decrease in the beta globulin fraction. A lowering of total neutral fat and elevation of phospholipids occurred concurrently. Minimal side effects were observed.

4. Heparin, 40,000 units given intravenously daily for one month, failed to influence the serum cholesterol level but did lower both the beta and gamma globulin. A decrease in serum neutral fat and a rise in phospholipid was noted.

5. Cytellin, 8 cc. before each meal, lowered the cholesterol, alpha-2, beta and gamma

globulin fractions, and decreased both the serum phospholipid and neutral fat.

6. The addition of desiccated thyroid, 2 gr. daily, to the cytellin regimen failed to alter the cholesterol. There was a decrease in albumin, and a rise in alpha-1, alpha-2 and beta globulin fraction. Serum phospholipids decreased and neutral fat rose slightly.

7. The addition of nicotinic acid, 3 gm. daily, produced marked gastrointestinal irritability only partially controlled by pro-banthine. There was some decrease in serum total cholesterol and in all globulin fractions.

*Acknowledgments:* I wish to express my appreciation to Dr. Thomas K. Hepler, Director of Pathology, Geisinger Memorial Hospital, Danville, Pennsylvania; Calvin Tice, Donald Mills and Beverly Kerrigan for the stenographic aid; and to Mr. Donald M. Yeager, Geisinger Memorial Hospital.

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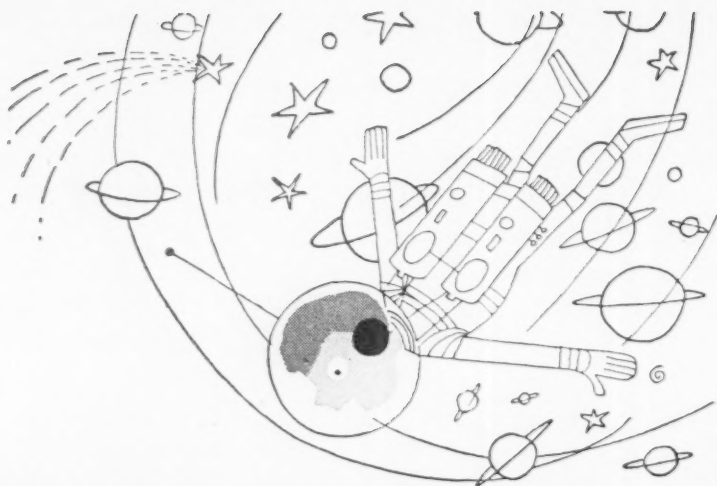
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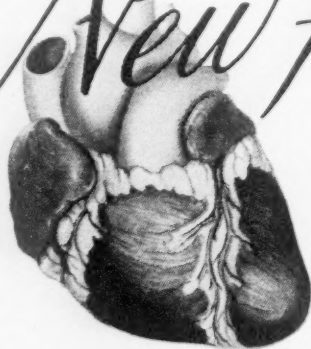
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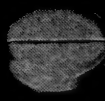
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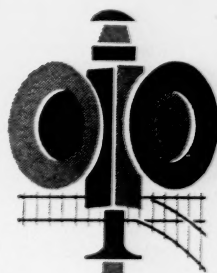
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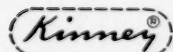
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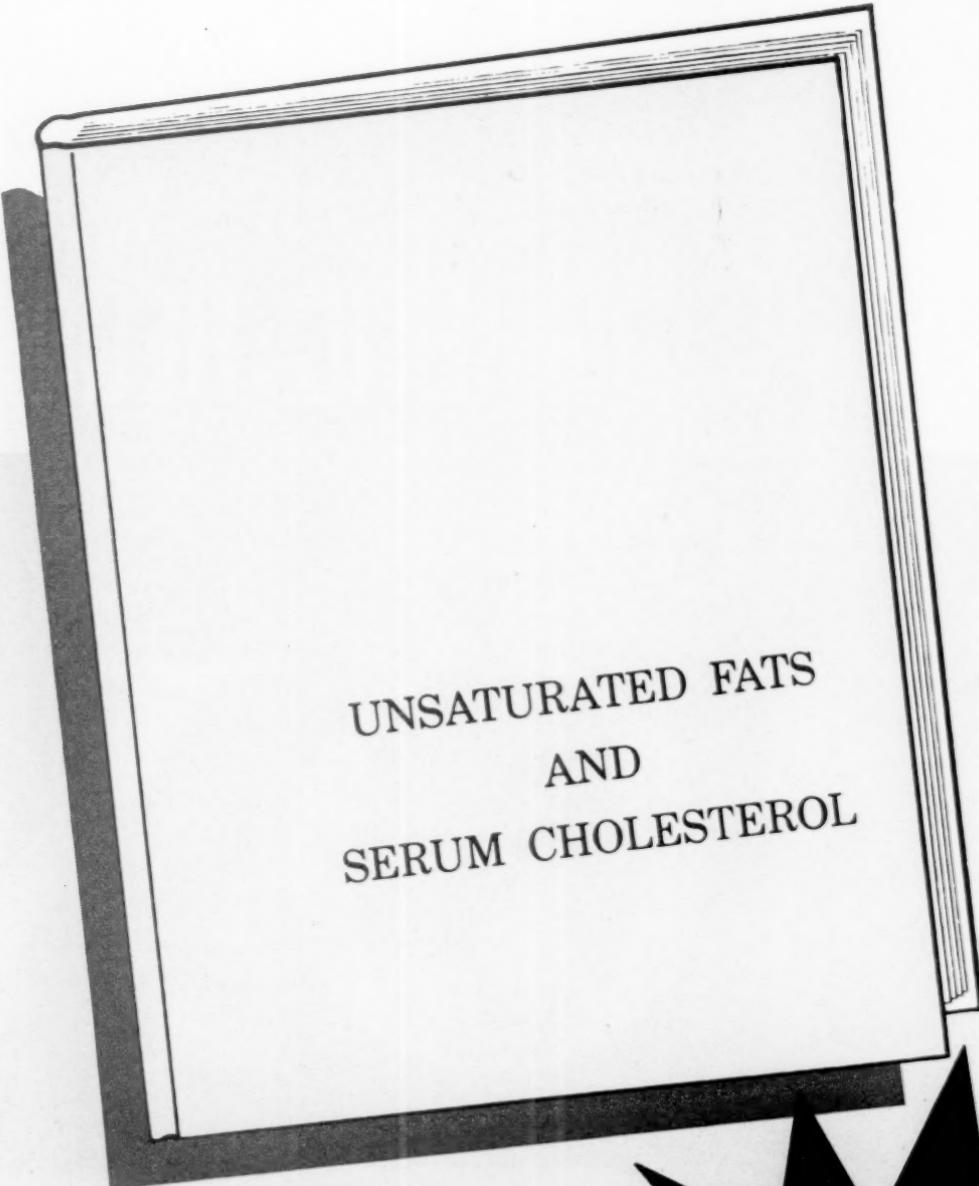
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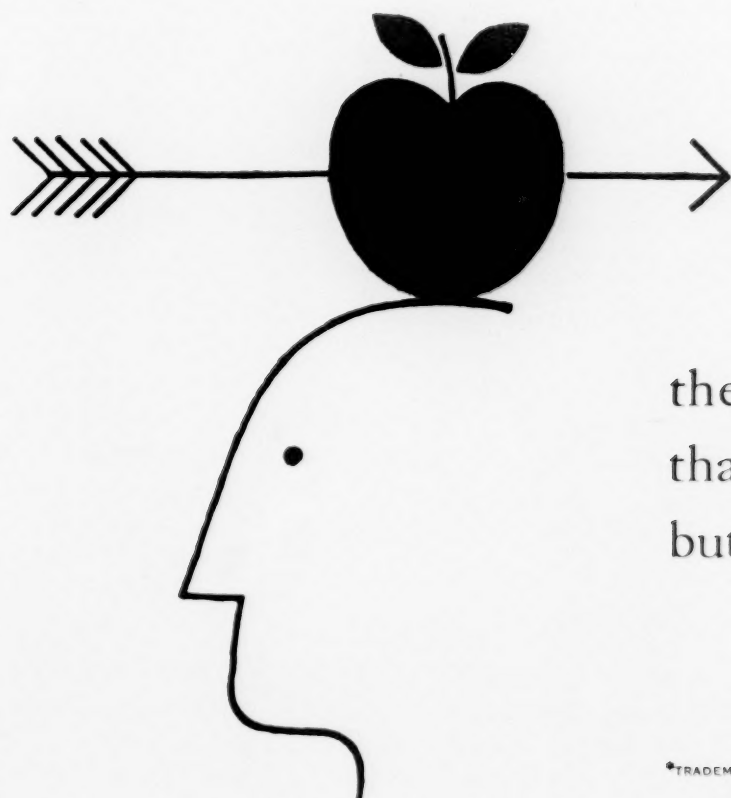
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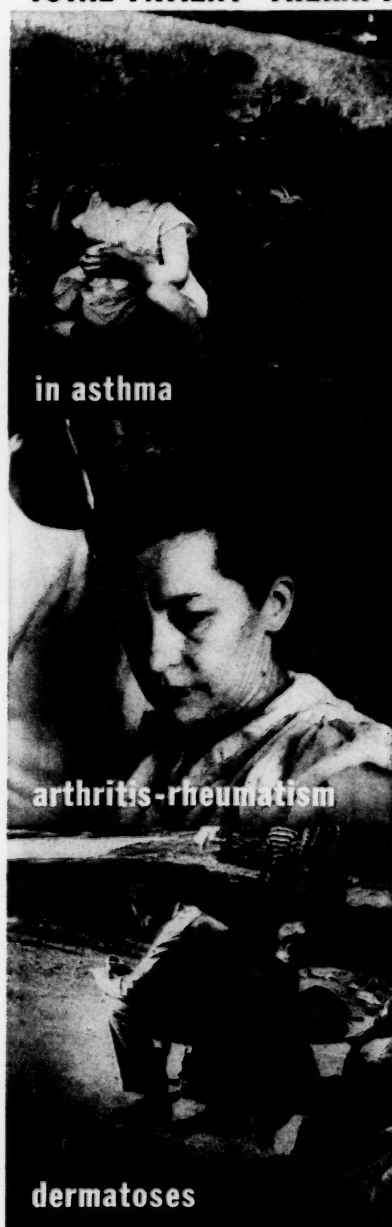
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prednisolone-hydroxyzine

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in asthma

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**EFFECTIVELY CONTROLS** anxiety-tension-induced exacerbations and emotional factors through the safe tranquilizer and muscle-relaxant<sup>1</sup> effects of hydroxyzine. Potentiates the action of prednisolone, markedly improving degree of response, sometimes doubling dosage efficiency, and permitting lower dosages.<sup>2-4</sup> The unique anti-secretory action<sup>5</sup> of hydroxyzine also minimizes corticoid-induced gastric reactions.

1. Hutcheon, D. E., et al.: Paper presented at Am. Soc. Pharmacol. & Exper. Therap., Nov. 8-10, 1956, French Lick, Ind.
2. Johnston, T. G., and Casort, A. G.: Clin. Rev. 1:17, 1958.
3. Warter, P. J.: J. M. Soc. New Jersey 54:7, 1957.
4. Individual Case Reports to Medical Dept., Pfizer Laboratories.
5. Strub, I. H.: To be published.

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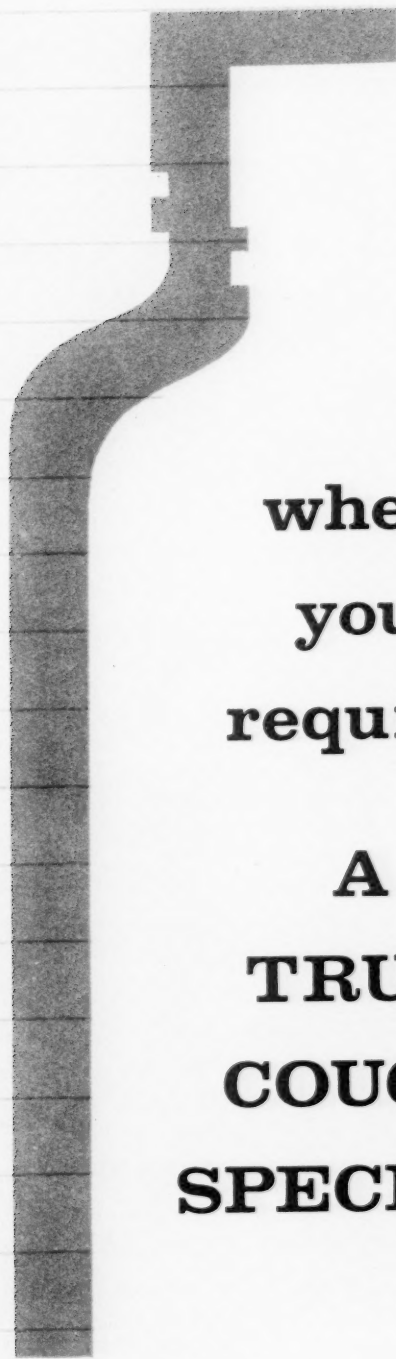
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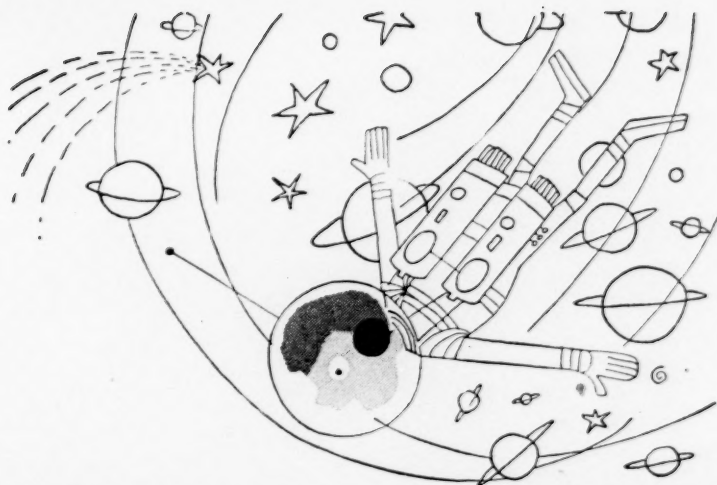
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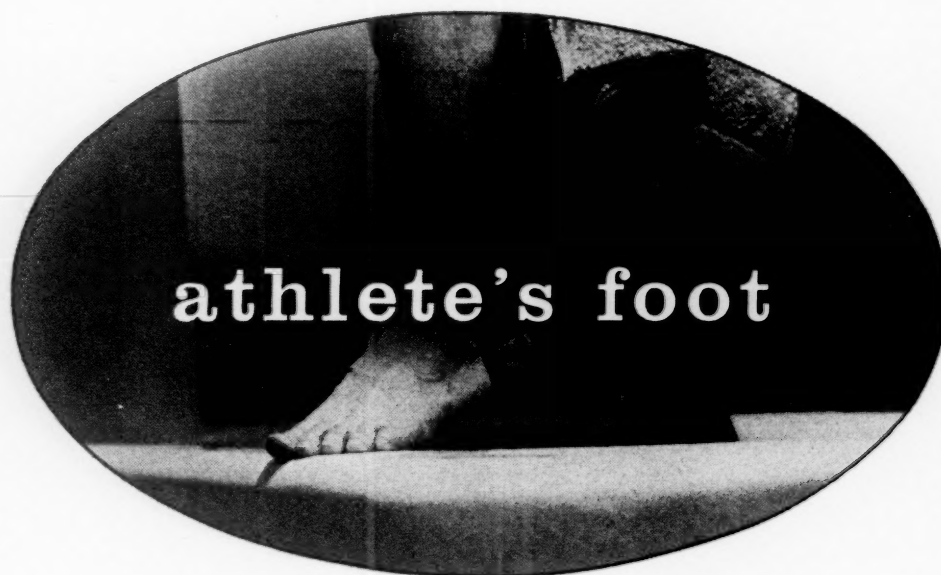
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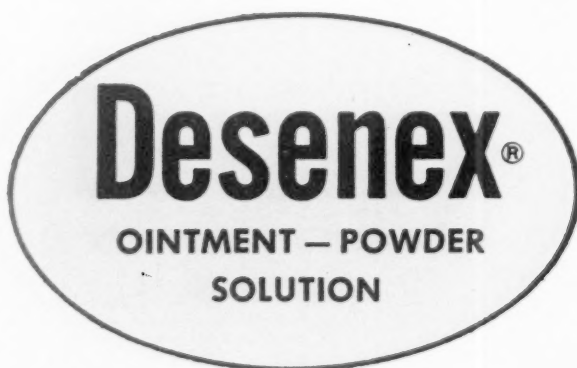
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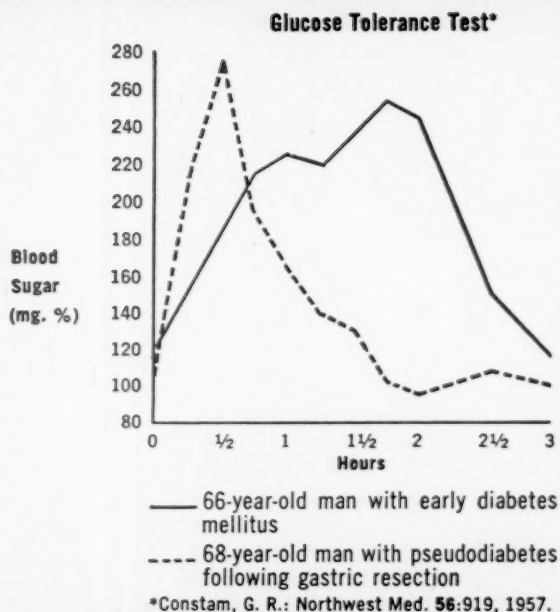
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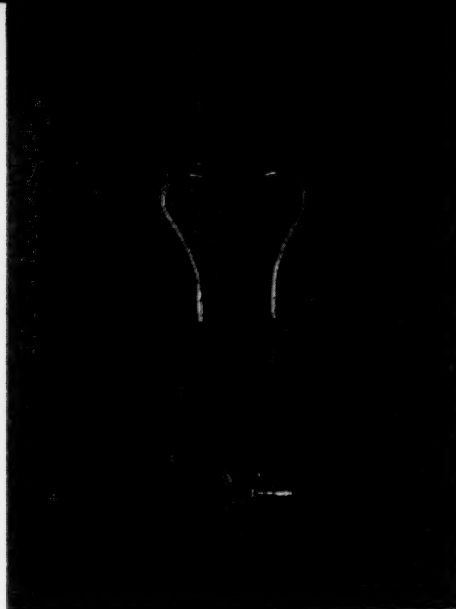
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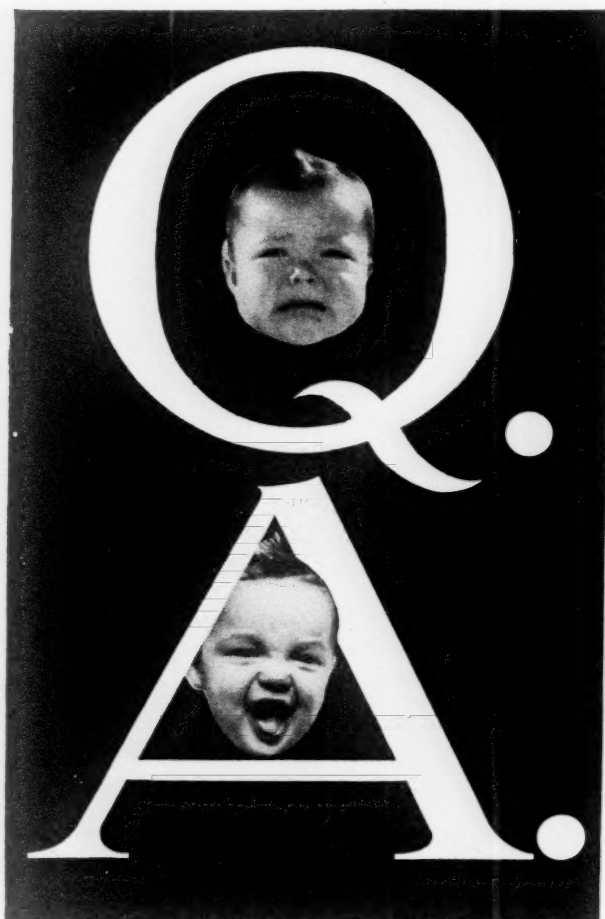
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1. Aravanis, C., and Luisada, A. A.: Am. J. Cardiology, in press.

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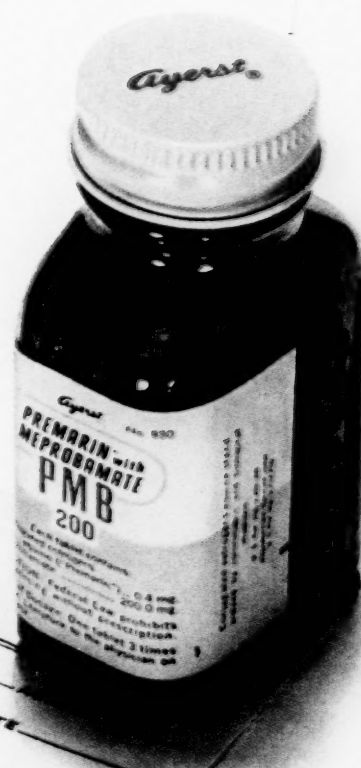
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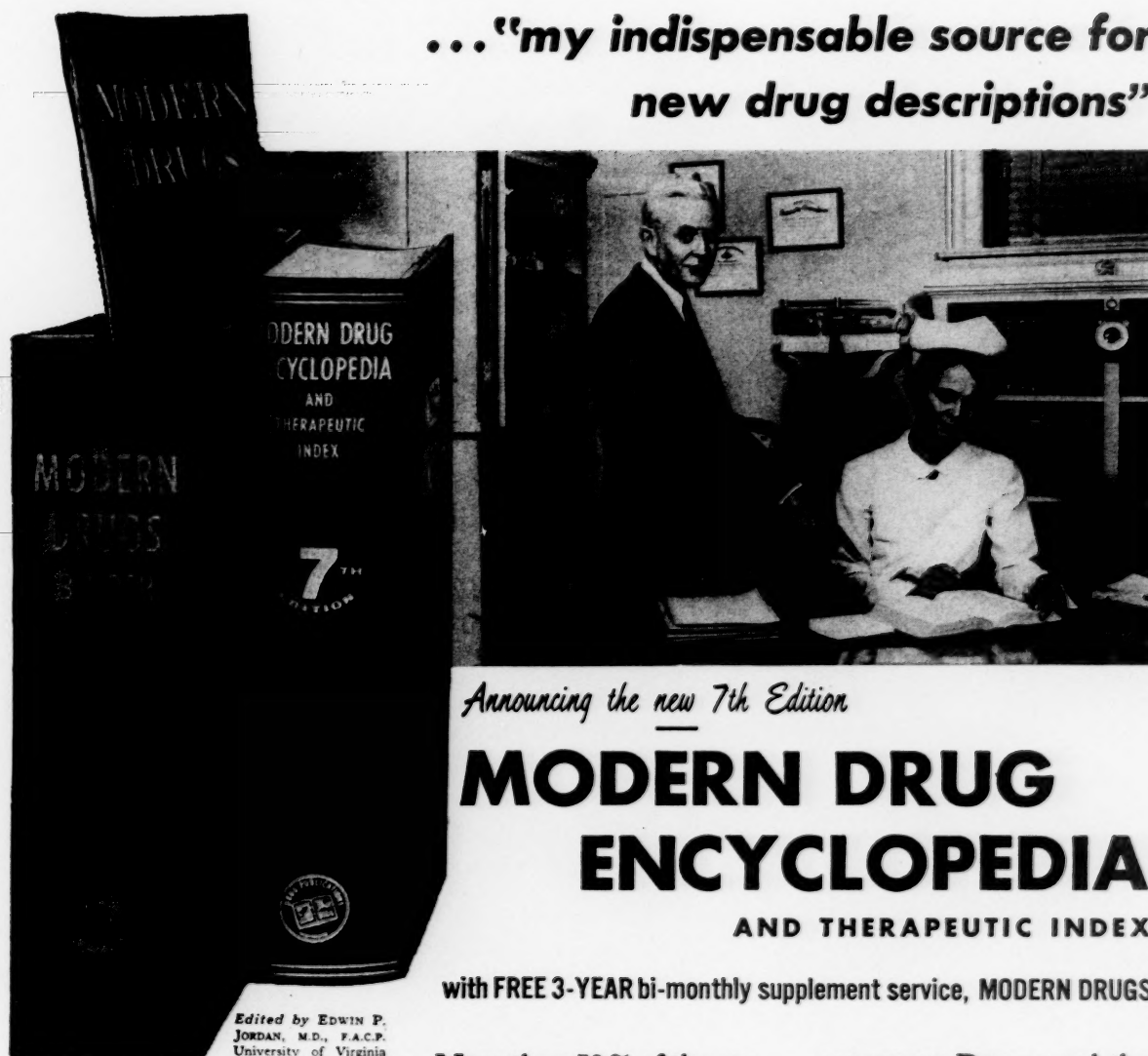


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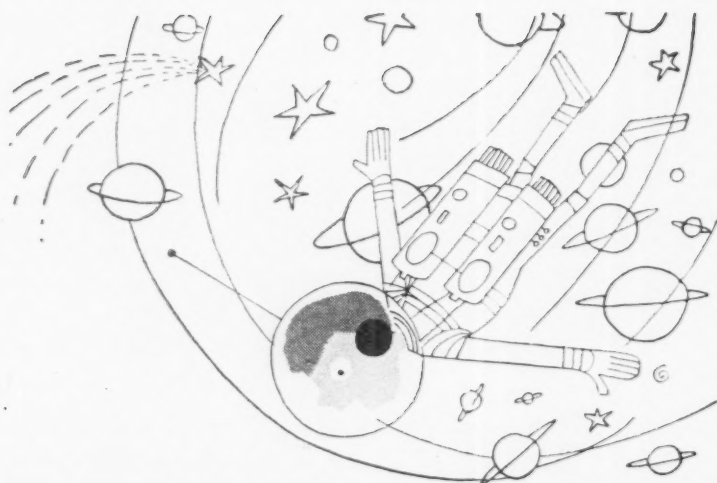
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**bibliography** 1. Rummel, W., and Candon, B. H.: Internat. Rec. Med. & G. P. Clin. 12:783, 1956. 2. Feldman, H. S., and Rummel, W.: M. Times 84:1329, 1956. 3. Dwyer, T. A.: Clin. Med. 4:457, 1957. 4. Pomeranze, J., and Gadek, R. J.: New England J. Med. 257:73, 1957. 5. Clancy, J. B.; Aldrich, R. H.; Rummel, W., and Candon, B. H.: Am. Pract. & Digest Treat. 8:1948, 1957. 6. O'Brien, T. E.; Onorato, R. R.; Dwyer, T. A., and Candon, B. H.: West. J. Surg. 65:29, 1957. 7. Frohman, I. P., and others: Scientific Exhibit, Sixth Congress Internat. Soc. Hemat., Boston, Mass., Aug. 26-Sept. 1, 1956. 8. Wagner, H.: Landarzt 31:496, 1955. 9. Jørgensen, G.: Arztl. Wehnschr. 10:82, 1955. 10. Aldrich, R. H.; Pomeranze, J.; Clancy, J. B., and others: Scientific Exhibit, A. M. A. Meeting, June, 1957, New York, N. Y.

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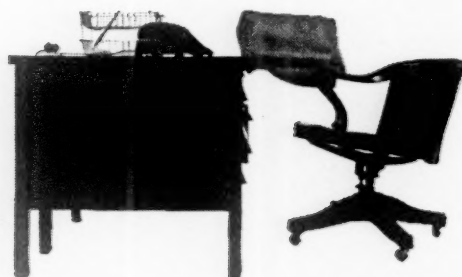
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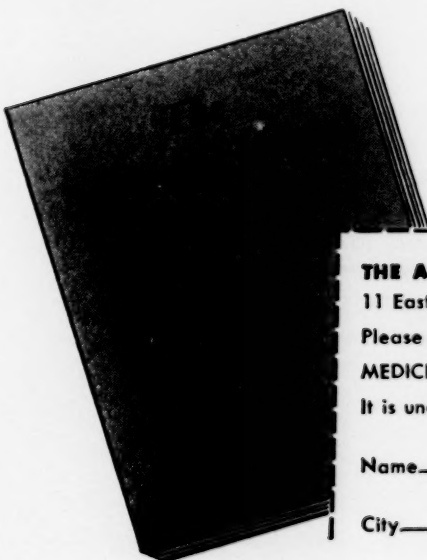
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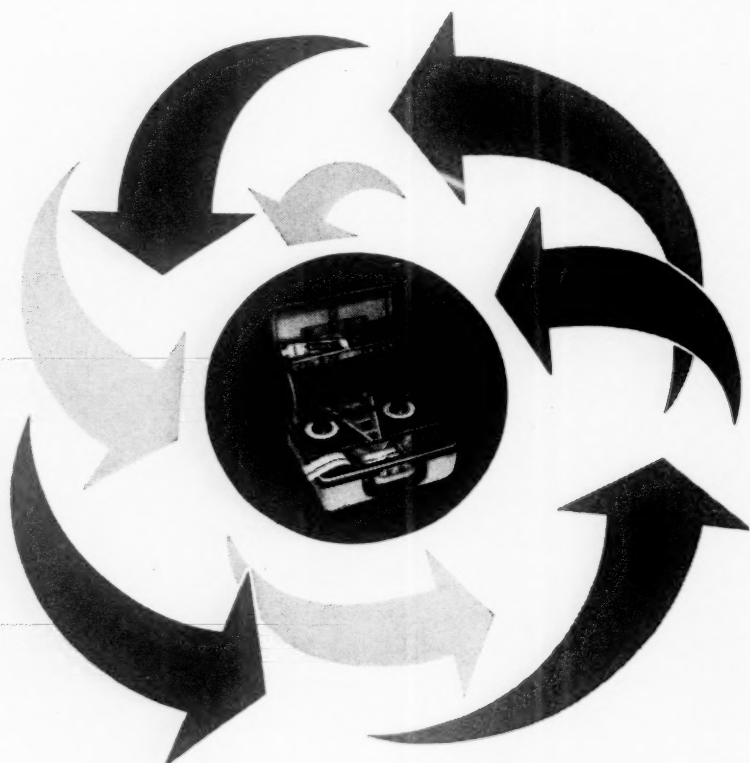
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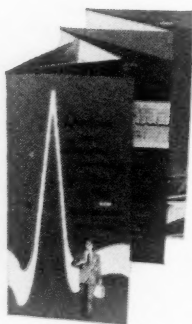
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\*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

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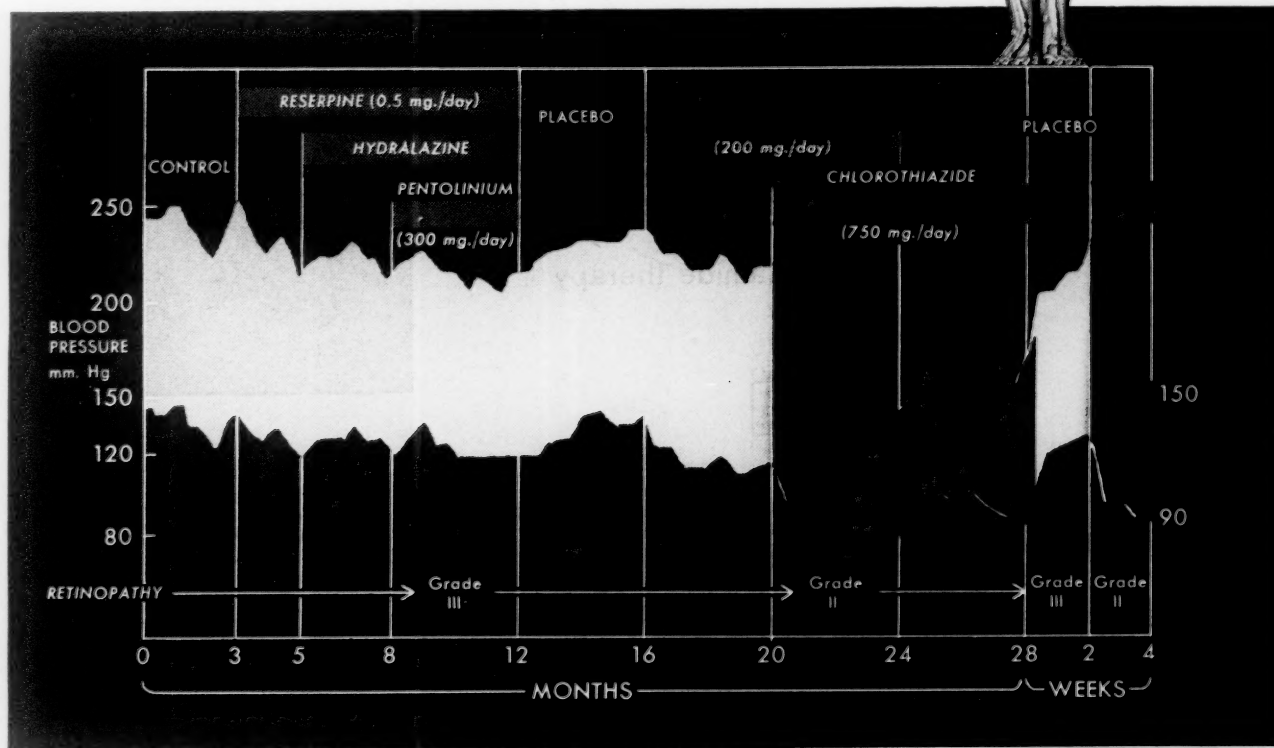
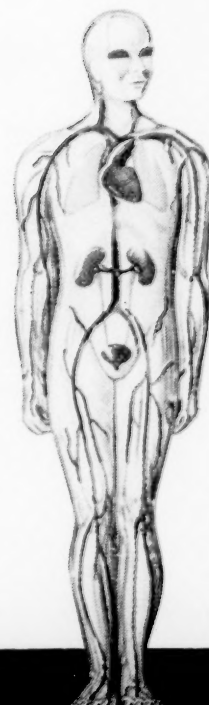
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Wilkins, R. W.: New England J. Med. 257:1026, Nov. 21, 1957.

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Freis, E. D., Wanko, A., Wilson, I. H. and Parrish, A. E.: J.A.M.A. 166:137, Jan. 11, 1958.

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In "Chlorothiazide: A New Type of Drug for the Treatment of Arterial Hypertension,"

Hollander, W. and Wilkins, R. W.: Boston Med. Quart. 8: 1, September, 1957.

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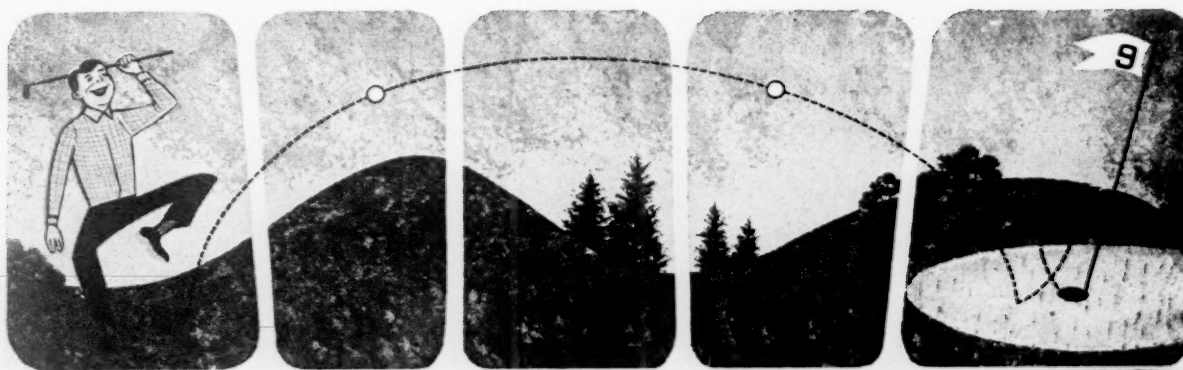
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2. Elman, R.: *J. Am. Dietet. Assoc.* 32:524 (June) 1956.



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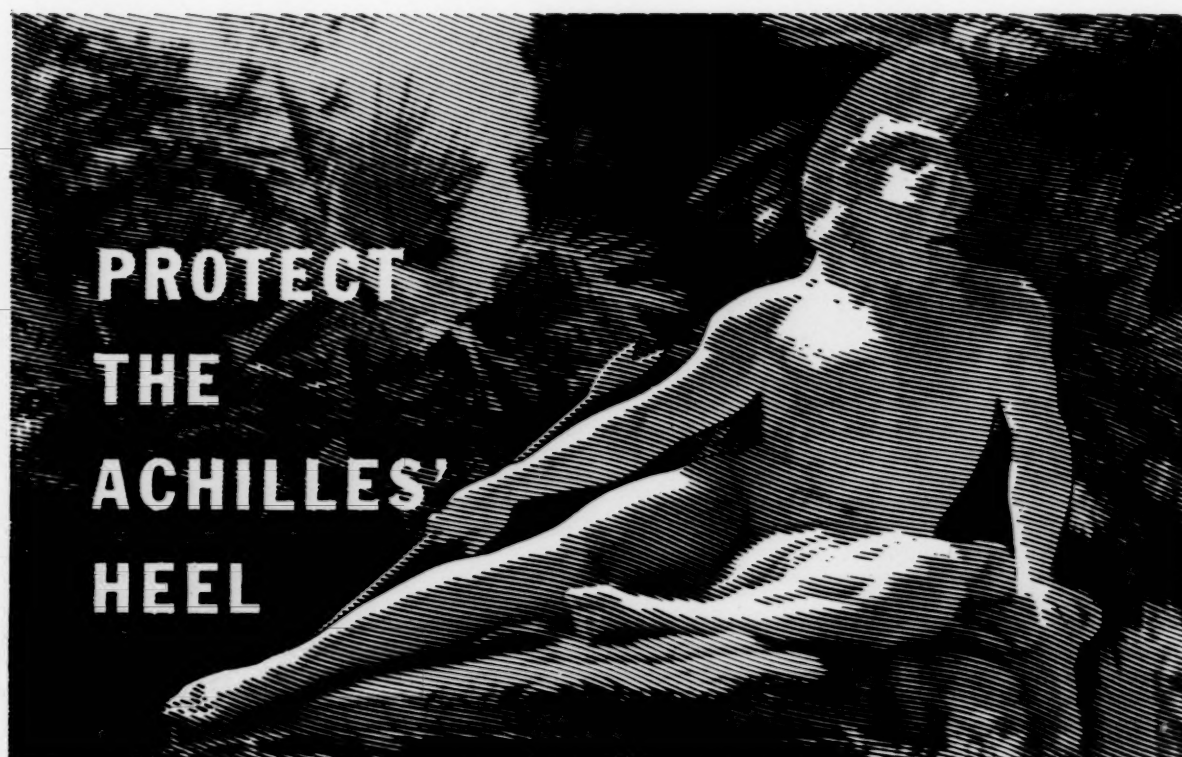
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1. M. Clin. North America 38:485 (March) 1954. 2. J.A.M.A. 162:1031, 1956. 3. J.A.M.A. 156:680, 1954. 4. Yale J. Biol. & Med. 28:308, 1955/56.



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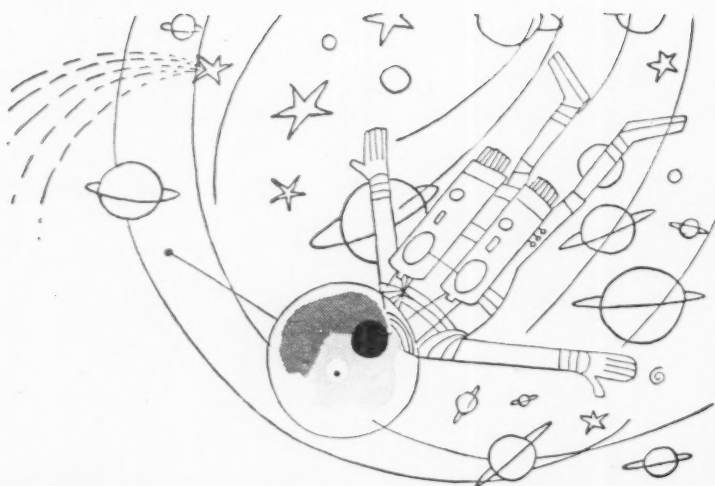
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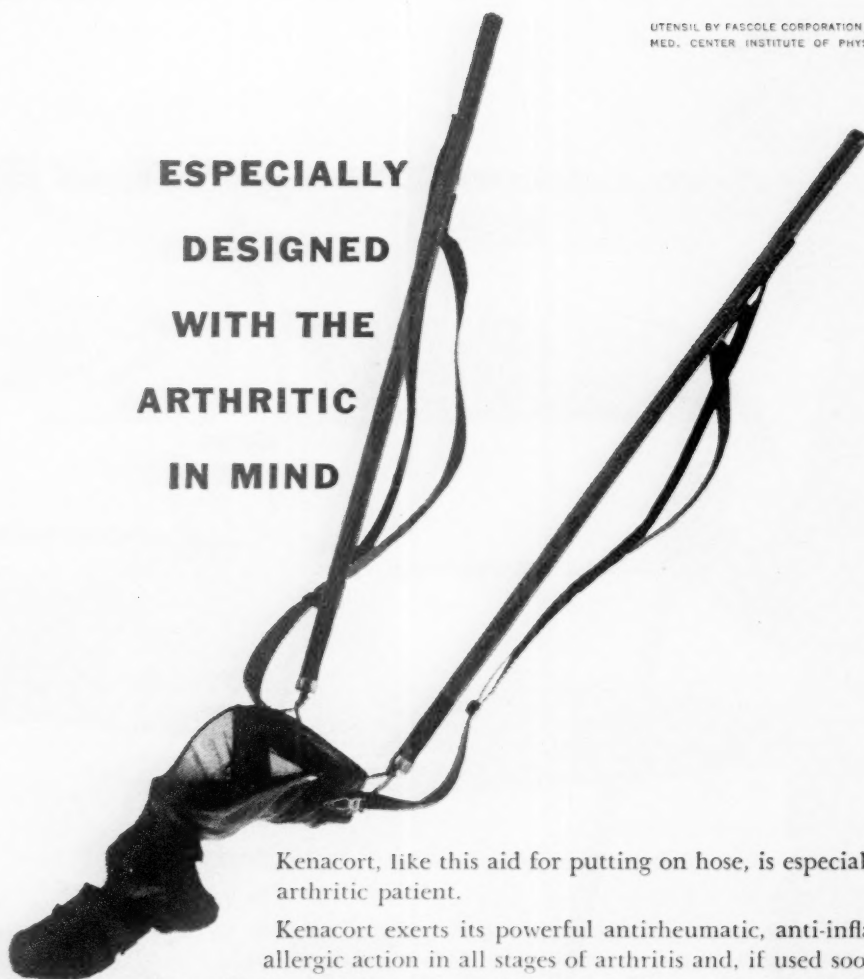
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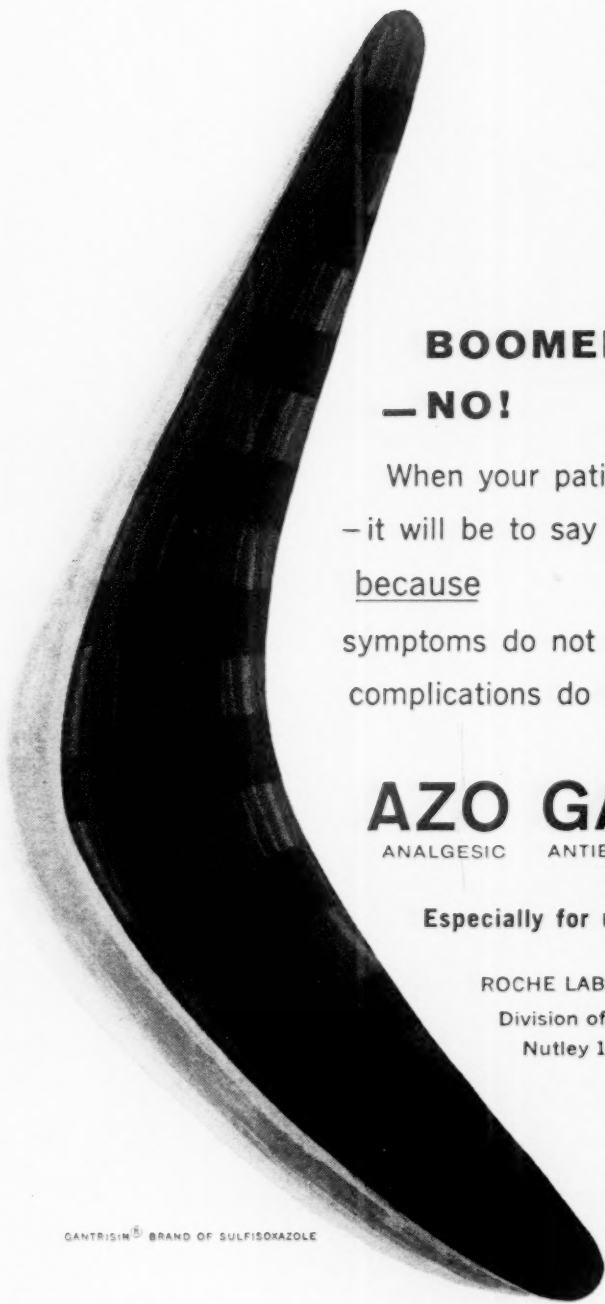


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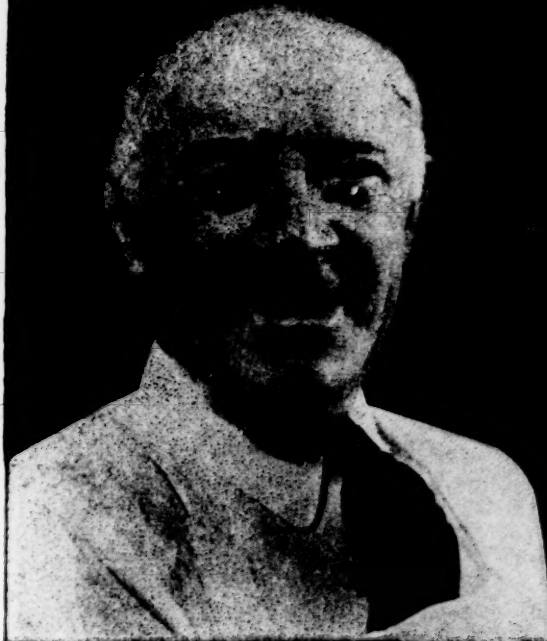
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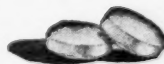
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